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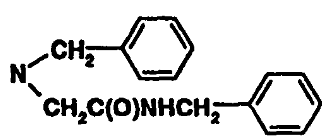
(54) Title: ANTIHERPES COMPOUNDS

(57) Abstract

Disclosed herein are compounds of the general formula X-Aryl-Y-Z wherein X is a five or six-membered aromatic heterocycle attached to an Aryl group, for example a phenyl group; Y is absent or a bridging group, for example $NHC(O)CH_2$; and Z is a terminal group, for example $NHC(O)OC(CH_3)_3$ or (I).



(I)

The compounds inhibit the herpes helicase-primase enzyme, rendering the compounds useful as antiviral agents. Also disclosed are pharmaceutical compositions comprising the compounds, as well as methods of preparing and using the compounds.

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ANTIHERPES COMPOUNDS

Technical Field of the Invention

This invention relates to methods for inhibiting herpes replication and for treating herpes infection in a mammal. In a preferred embodiment, this invention relates to compounds that inhibit the herpes helicase-primase enzyme complex. This invention also relates to pharmaceutical compositions comprising the compounds, to methods of using and producing the compounds.

Background of the Invention

Herpesviruses inflict a wide range of diseases against humans and animals. For instance, herpes simplex viruses, types 1 and 2 (HSV-1 and HSV-2), are responsible for cold sores and genital lesions, respectively; varicella zoster virus (VZV) causes chicken pox and shingles; and the human cytomegalovirus (HCMV) is a leading cause of opportunistic infections in immunosuppressed individuals.

Herpesviruses are complex double-stranded DNA viruses that encode all the enzymes that directly mediate viral chromosomal replication. Seven DNA replication-associated polypeptides are required for human herpesvirus replication. Six of these seven polypeptides show a high degree of homology across all studied human herpesviruses. These six polypeptides, when expressed by the virus, constitute a heterodimeric DNA-dependent DNA polymerase, a monomeric single-stranded DNA binding protein, and a heterotrimeric helicase-primase complex. The seventh DNA replication-associated polypeptide does not display sequence or functional conservation and is involved in the initiation of lytic viral replication.

Without the function of each of the seven herpesvirus-specific DNA replication proteins, herpesvirus chromosomal replication will not initiate or propagate. This has been demonstrated in two ways for DNA replication in

HSV-1. First, temperature sensitive HSV-1 strains have been developed and the complementation groups within these strains mapped on a one-to-one correspondence to the seven HSV DNA replication genes. Additionally, transient replication assays that utilized recombinant DNA plasmids containing single DNA replication genes have found that the presence of each of the seven genes was required for the efficient replication of a tester plasmid containing an HSV-1 origin of DNA replication.

More recently, the DNA replication genes in other herpesviruses (i.e., Epstein-Barr virus, cytomegalovirus and varicella zoster virus) have been delineated. These gene sequences were identified as homologous to the HSV-1 DNA replication genes. Furthermore, transient replication assays containing either an Epstein-Barr virus or cytomegalovirus lytic origin of DNA replication confirmed their identity. In varicella zoster virus (the human herpesvirus most closely related to HSV-1) DNA replication genes were found to be highly homologous to HSV-1 (>50% at the amino acid level) and present at identical relative locations on the two viral chromosomes. Although no follow-up analysis on varicella zoster virus DNA replication genes has been presented to date, it is highly unlikely that differences in the varicella zoster virus and HSV-1 DNA replication programs exist.

From the above, it is clear that human DNA replication proteins are unable to substitute for the HSV-1 encoded enzymes. Otherwise, temperature-sensitive viral polypeptides would have been complemented by human counterparts and the defective viruses would have continued to grow and replicate, even at elevated temperatures. Similarly, in transient replication assays, if human proteins were capable of complementing any of the seven herpesvirus-encoded polypeptides, an absolute dependence on the presence of each of these herpesvirus DNA replication-specific genes would not have been observed. Therefore, inhibiting the activity of those virally-encoded proteins represents an effective way of preventing herpesviral replication.

The helicase-primase enzyme occupies a key and critical place in the herpesvirus DNA replication program. The observation that the genes encoding the herpes helicase-primase are not only essential for replication, but are also highly conserved across the range of known herpesviruses underscores the importance of this enzyme in mediating viral chromosomal replication.

In the helicase-primase complex, two of the three polypeptides (e.g., the expression products of the UL5 and UL52 genes of HSV-1) promote catalysis of duplex DNA unwinding and RNA primer biosynthesis. The third polypeptide, encoded by the UL8 gene, appears to modulate primase activity. The assembled helicase-primase enzyme complex functions both in the initiation and propagation stages of herpesvirus DNA replication. It is responsible for the synthesis of RNA primers necessary for the initiation of all new DNA synthesis by the herpesvirus DNA polymerase. Additionally, for DNA replication to proceed, duplex viral chromosomal DNA must first be unwound to the single-stranded replicative intermediate because the herpesvirus DNA polymerase is inactive on fully duplex DNA. The helicase-primase is also responsible for this important DNA unwinding event.

Conventional anti-herpes therapies have not focused on inhibiting the activity of the herpes helicase-primase(see R.E. Boehme et al., Annual Reports in Medicinal Chemistry, **1995**, *30*, 139). The most widely used anti-herpes agents to date are purine and pyrimidine nucleoside analogs, such as acyclovir and ganciclovir. These nucleoside analogues inhibit replication of viral DNA by their incorporation into a growing DNA strand. The nucleoside analogue-based inhibitors of HSV-1 growth have found only limited success and are not generally useful in treating recurring infections in the majority of patients. In addition, the infection of humans by other herpesviruses, such as varicella zoster virus or cytomegalovirus, show little or no responsiveness to nucleoside-based therapies.

The lack of broad spectrum anti-herpesvirus activity by the nucleoside-based therapies is not surprising because these compounds act by indirect

biological mechanisms. Nucleoside analogues must first be activated to the nucleoside monophosphate by a virally-encoded thymidine kinase enzyme. It should be pointed out that only HSV and varicella zoster virus encode thymidine kinase enzymes. This may, in part, explain the inability to adapt nucleoside-based therapies to the treatment of other human herpesviruses. After initial phosphorylation, the nucleoside analogue monophosphate must be further phosphorylated to the triphosphate by human-encoded enzymes prior to its action. Ultimately, the triphosphorylated nucleoside analogue is incorporated into a nascent DNA chain during viral genomic replication, thereby inhibiting the elongation of that DNA chain by the herpes DNA polymerase.

The final incorporation step of the nucleoside-based therapies has been characterized as "competitive" because the herpes DNA polymerase does not display a preference for the activated nucleoside drug versus normal deoxynucleoside triphosphates. However, because the action of the DNA polymerase is not considered rate-limiting for herpesvirus DNA replication, the utility of nucleoside-derived compounds in treating herpesvirus infections is necessarily limited. Accordingly, the need for effective, safe therapeutic agents for treating herpesvirus infections continues to exist.

Y. Kawamatsu et al., Eur. J. Med. Chem.-Chimica Therapeutica, **1981**, *16*, 355;
K.D. Hargrave et al., J. Med. Chem., **1983**, *26*, 1158;
T. Nakao et al., Japanese patent application 63-060978, published September 1, 1986; Chem. Abstr., **1989**, *110*, 716, 135228r;
C.G. Caldwell et al., US patent 4,746,669, issued May 24, 1988;
J.A. Lowe, European patent application 279,598, published August 24, 1988;
A.A. Nagel, European patent application 372,776 published June 13, 1990;
J.A. Lowe et al., J. Med. Chem., **1991**, *34*, 1860;
A. Bernat et al., Canadian patent application 2,046,883, publisehd June 30, 1991;
A. Wissner, US patent 5,077,409, issued December 31, 1991;

Y. Katsura et al., European patent application 545,376, published June 9, 1993;
J.E. Macor and J.T. Nowakowski, PCT patent application WO 93/18032, published September 16, 1993;
D.I.C. Scopes et al., UK patent application 2,276,164, published September 21, 1994;
A. Leonardi et al., PCT patent application WO 95/04049, published February 9, 1995;
G.D. Hartman et al., PCT patent application WO 95/32710, published December 7, 1995;
J.J. Crute et al., PCT patent application WO 97/24343, published July 10, 1997;
C.N. Selway and N.K. Terret, Bioorganic & Medicinal Chemistry, **1996**, *4*, 645; and
F.C. Spector et al., J. Virol. **1998**, *72*, 6979.

The present non-nucleoside-based compounds can be distinguished from the prior art compounds by their different chemical structures and biological activities.

Summary of the Invention

The invention described herein overcomes the above-mentioned limitations and satisfies the above-mentioned needs by providing non-nucleoside-based compounds, which are inhibitors of herpes viral replication, such as for example inhibitors that act directly in interfering with the likely rate-limiting process in herpesvirus DNA replication: the action of the helicase-primase enzyme. Furthermore, since the herpesvirus helicase-primase enzyme is conserved across the human herpesviruses, such compounds of this invention are effective against the full spectrum of herpesviruses, including HSV, varicella zoster virus and cytomegalovirus, and also against nucleoside-nonresponsive and nucleoside-resistant herpes infections.

The non-nucleoside-based compounds may be characterized by having a five- or six-membered heterocycle attached to a phenyl or pyridinyl ring. Compounds possessing such a moiety have been reported previously, for example:

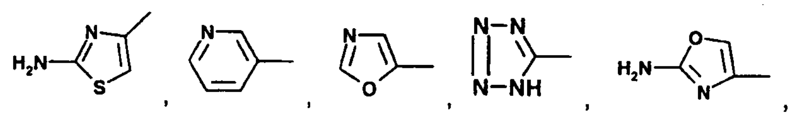
The non-nucleoside-based compounds are represented by formula 1

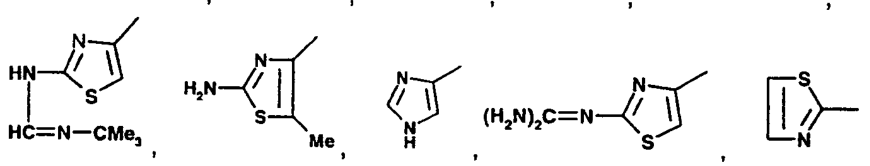
X-Aryl-Y-Z (1)

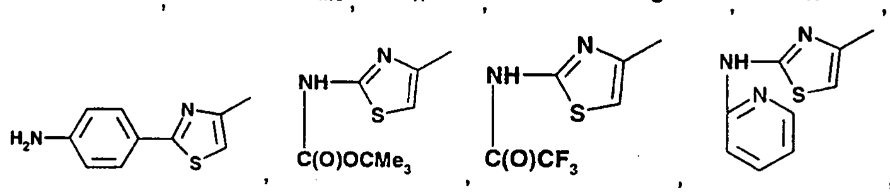
wherein

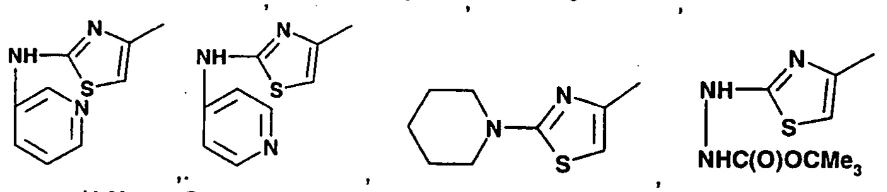
(i) **X** is selected from the group consisting of:

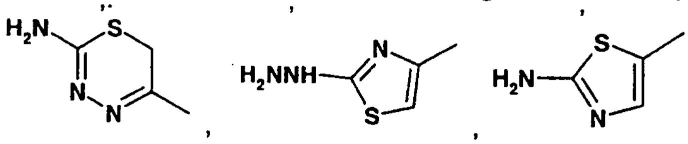
H, $H_2NC(O)NHCHMe$, $NH_2S(O)_2$—,











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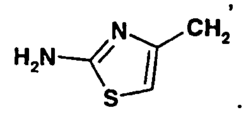
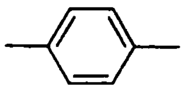
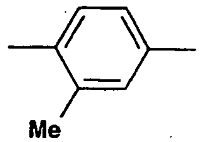
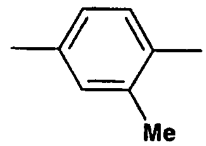
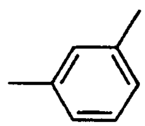
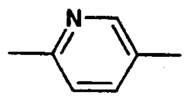
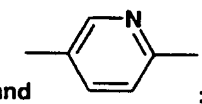


;

Aryl is selected from the group consisting of:

, , ,

,  and ;

Y is $\overset{R^2}{\overset{|}{N}}-C(O)-\overset{R^3}{\overset{|}{CH}}$ wherein

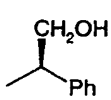
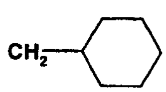
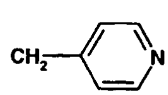
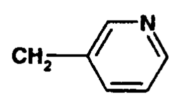
R² is H or lower alkyl, and

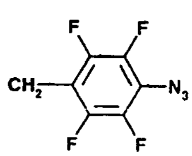
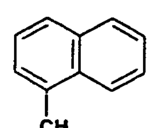
R³ is H; lower alkyl; (lower cycloalkyl)-(lower alkyl) (e.g. CH_2-(cyclohexyl); phenyl(lower alkyl); phenyl(lower alkyl) monosubstituted, disubstituted or trisubstituted on the aromatic portion thereof with a substituent or substituents selected independently from the group consisting of halo, hydroxy, lower alkoxy, lower alkoxy, lower alkyl, azido and trifluoromethyl; CH_2-Het; or CH_2-(bicyclic heterocyclic system); and

Z is NR^4R^5 wherein

R⁴ is H, phenyl(lower alkyl) (e.g. CH_2Ph) or phenyl(lower alkyl) monosubstituted, disubstituted or trisubstituted on the aromatic portion thereof with a substituent or substituents selected independently from the group consisting of halo, hydroxy, lower alkoxy, lower alkyl, azido and trifluoromethyl, or

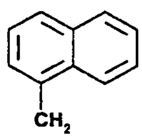
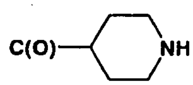
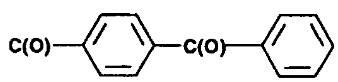
R⁴ is selected from the group consisting of:

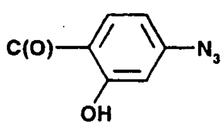
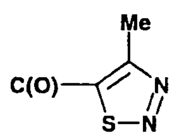
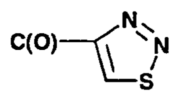
, , , ,

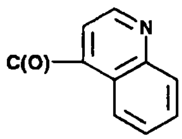
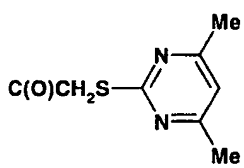
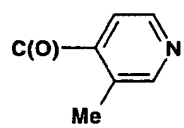
 and ;

and R^5 is selected from the group consisting of:

$C(O)(CH_2)_5NH_2$; $CH_2C(O)N(Me)CH_2Ph$; $CH_2C(O)NHCH_2Ph$; $C(O)CH_2OH$;

 ;  ;  ;

 ;  ;  ;

 ;  and  ;

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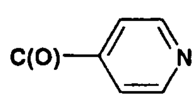
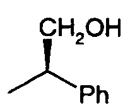
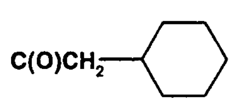
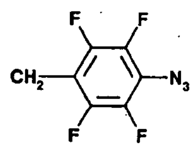
 ,

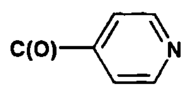
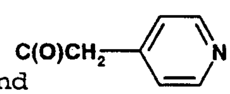
when R^4 is  or a mono-, di- or trisubstituted phenyl(lower alkyl) wherein each substituent is on the aromatic portion and is selected independently from azido and trifluoromethyl;

or R^5 is

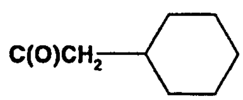
 ,

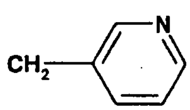
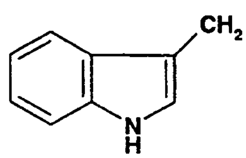
when $\mathbf{R}^4$ is  or a mono-, di- or trisubstituted phenyl(lower alkyl) wherein each substituent is on the aromatic portion and is selected independently from azido and trifluoromethyl;

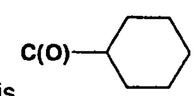
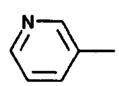
or $\mathbf{R}^5$ is selected from the group consisting of:

C(O)Ph,  and ,

when $\mathbf{R}^3$ is CH_2-(cyclohexyl);

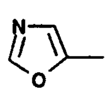
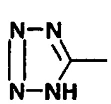
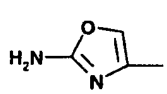
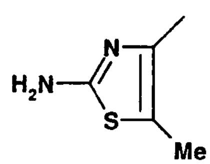
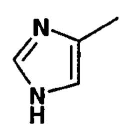
or $\mathbf{R}^5$ is  or C(O)OCMe$_3$ when $\mathbf{R}^3$ is $CH_2CH_2CH_2NH_2$,

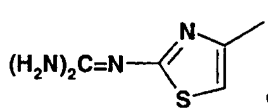
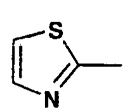
 or  ;

or $\mathbf{R}^5$ is , when **X** is  ;

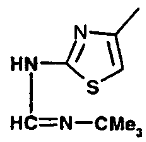
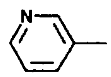
or $\mathbf{R}^5$ is C(O)Ph,

when **X** is $NH_2S(O)_2$, $H_2NC(O)NHCHMe$,

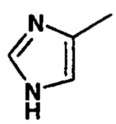
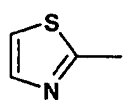
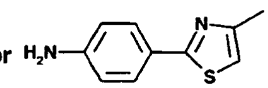
, , , , ,

 or  ;

or R^5 is phenyl(lower alkyl) or mono-, di- or trisubstituted phenyl(lower alkyl) wherein each substituent is on the aromatic portion and is selected independently from azido and trifluoromethyl,

when **X** is  or  ;

or R^5 is $C(O)OCMe_3$,

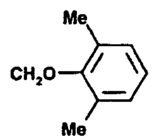
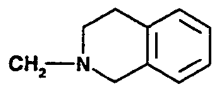
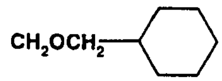
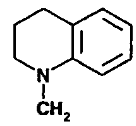
when **X** is  ,  or  ;

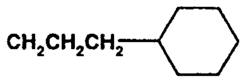
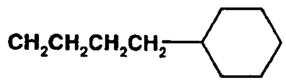
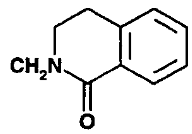
or

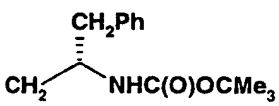
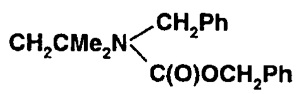
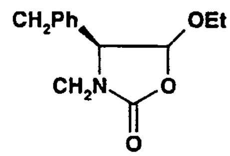
(ii) **X** and **Aryl** are as defined above;

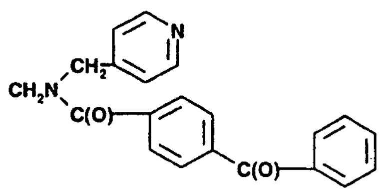
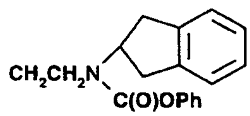
Y is $\overset{R^2}{\overset{|}{N}}\text{—C(O)}$ wherein R^2 is H or lower alkyl, and

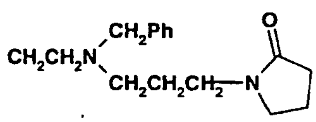
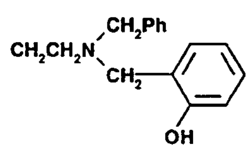
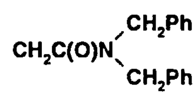
Z is selected from the group consisting of:
CH_2OCH_2Ph, CH_2OPh, OCH_2CHMe_2, CH_2CH_2Ph, $CH_2CH_2CH_2Ph$, CH_2SCH_2Ph, $CH{=}CHPh$, $CH_2CH_2CH_2CH_2C(O)NPh_2$, $CH_2CH_2CH_2CH_2CH_2NH_2$, $CH_2CH_2NH_2$, $CH(NH_2)(CH_2)_4NHC(O)OCH_2Ph$, (*S*)-$CH(NHCH_2Ph)(CH_2)_4NHC(O)OCH_2Ph$, (*S*)-$CH_2C(O)NHCH(Me)Ph$, (*R*)-$CH(NH_2)(CH_2)_4NHC(O)OCH_2Ph$, $CH_2CH_2NH_2$, $CH_2CH_2NHC(O)CH_2N(CH_2Ph)_2$, $CH_2CH_2NHC(O)N(CH_2Ph)_2$, $CH_2CH_2CH_2C(O)N(CH_2Ph)_2$, $CH_2CH_2C(O)N(CH_2Ph)_2$,

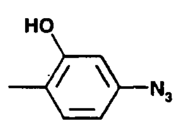
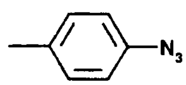
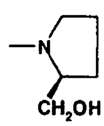
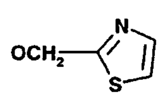
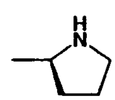
, , , ,

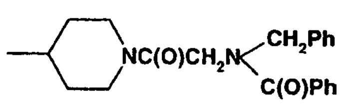
, , ,

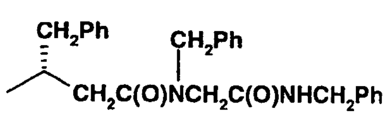
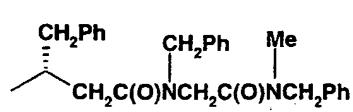
, , ,

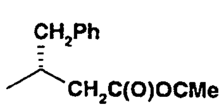
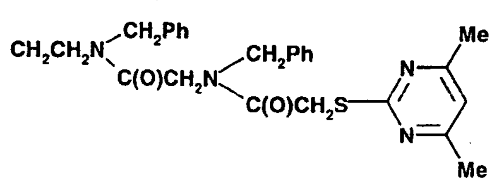
, ,

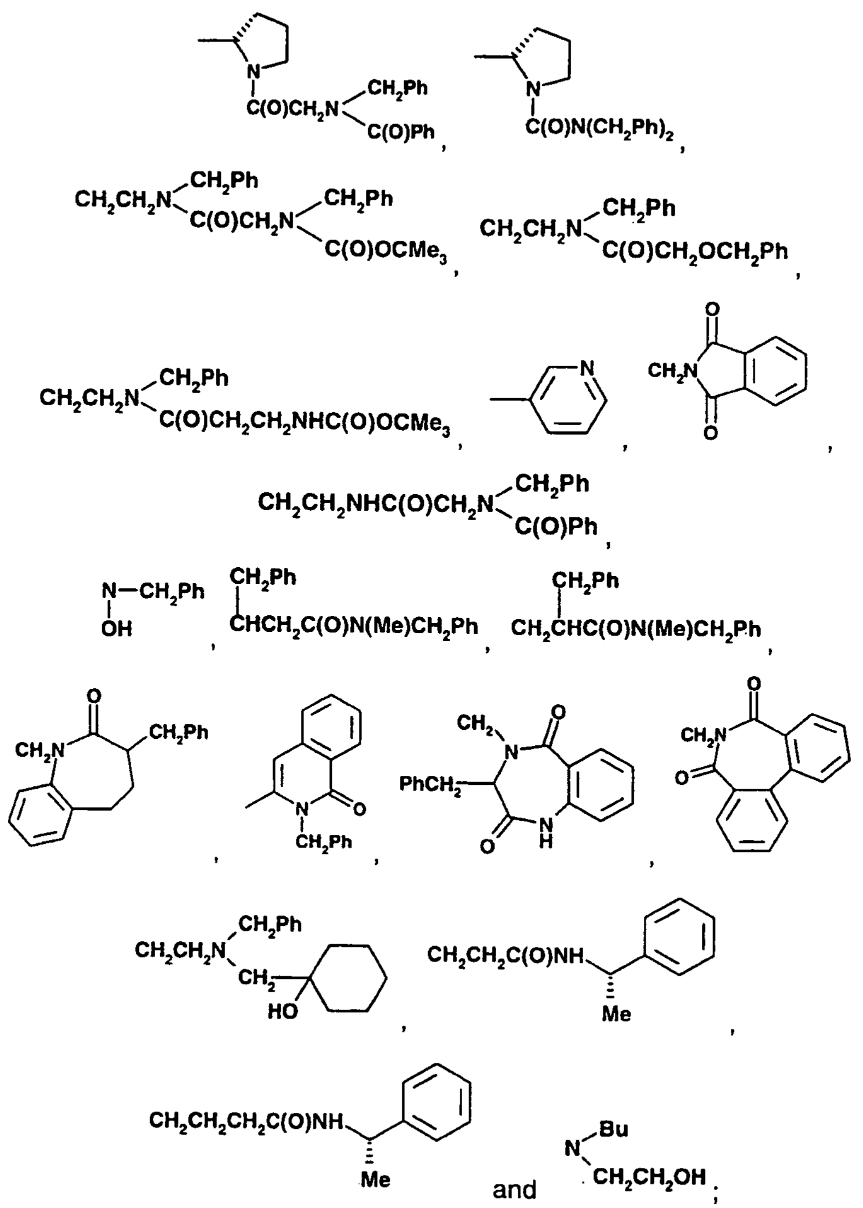
, , ,

, , , , ,

,

(*S*)- , ,

, ,

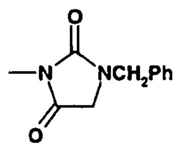
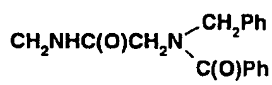
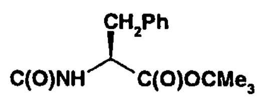


or

(iii) **X** and **Aryl** are as defined above;

Y is absent (i.e. a valence bond); and

Z is selected from the group consisting of:
$NHCH_2C(O)N(Me)CH_2Ph$, $NHCH_2C(O)NHCH_2Ph$, $OCH_2C(O)N(Me)CMe_3$, $OCH_2C(S)NHCH_2Ph$, $NHC(S)NHCH_2Ph$, $C(O)OMe$, $CH_2CH_2NH\text{-}S(O)_2\text{-}CH_2Ph$, $CH_2CH_2NHC(O)CH_2CH_2C(O)Ph$, $CH_2CH_2N(CH_2Ph)C(O)CH_2Ph$, $CH_2CH_2N(CH_2Ph)S(O)_2CH_2Ph$, $CH_2CH_2NHC(O)CH_2CH_2C(O)NHCH_2Ph$, $CH_2CH_2NHC(O)CH_2NHC(O)OCMe_3$, $CH_2CH_2NHCH_2C(O)N(CH_2Ph)_2$, $CH_2NHCH_2C(O)N(CH_2Ph)_2$,


, 
, 
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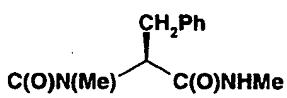
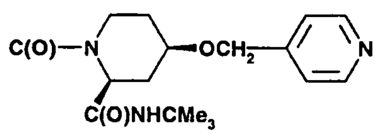

, 
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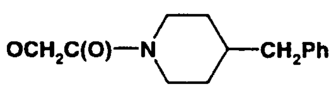
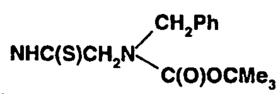

, 
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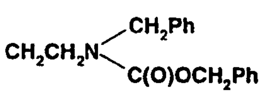
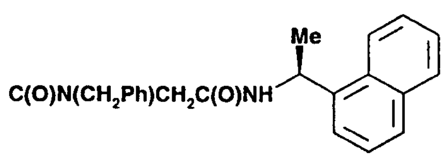

, 
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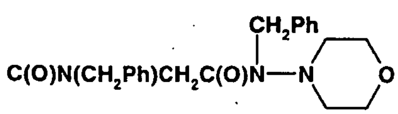
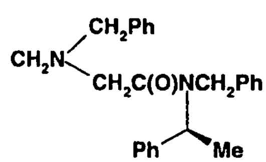

, 
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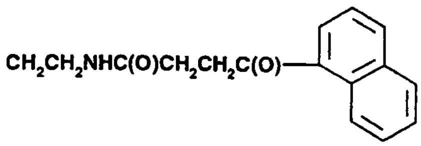
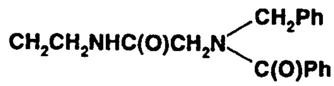
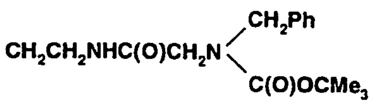
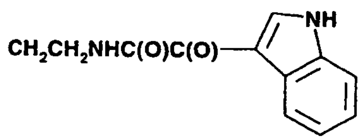
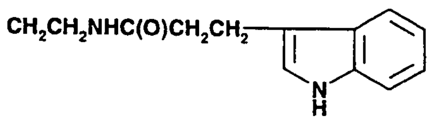
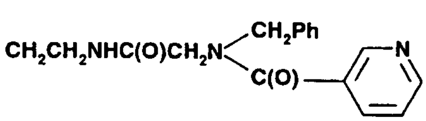
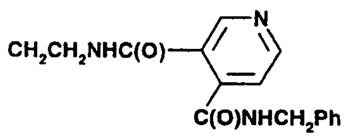
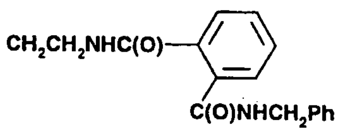
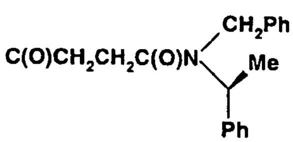
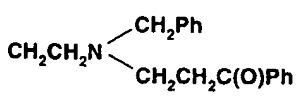
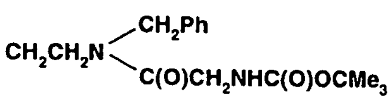
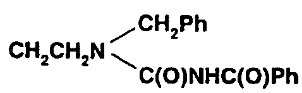
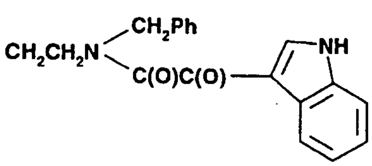
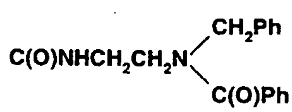
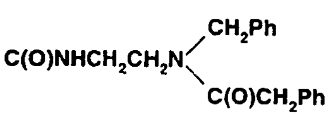
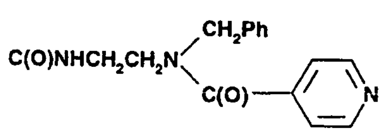
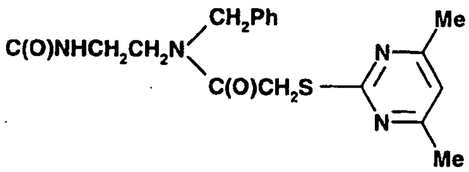
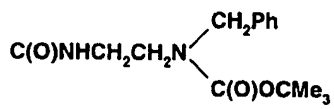
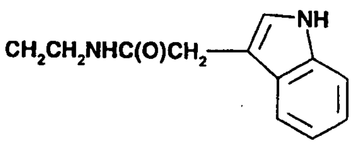
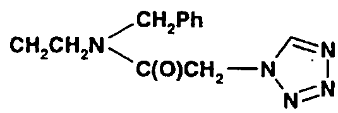
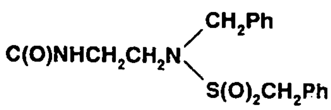
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,

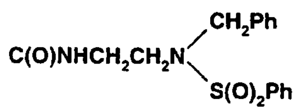
,

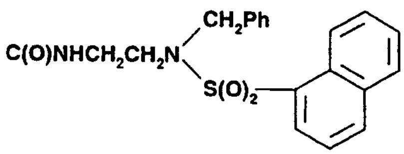
,

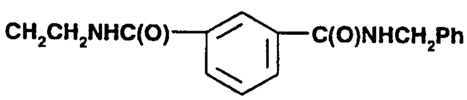
,

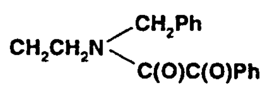
,

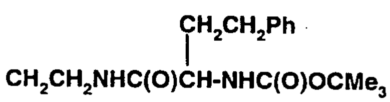
,

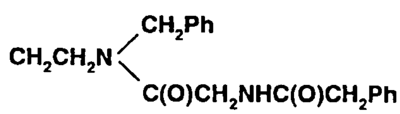
,

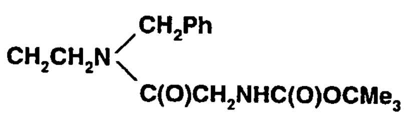
,

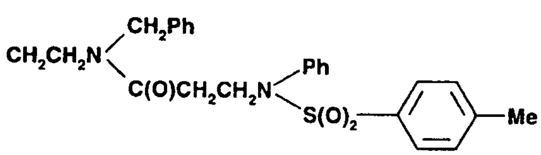
,

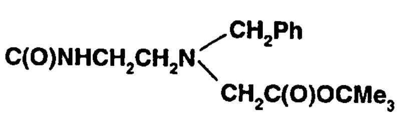
,

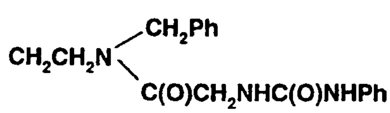
,

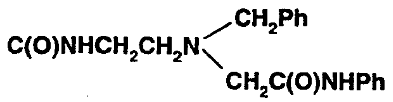
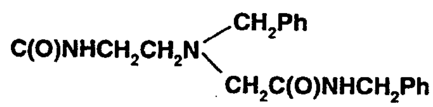
,

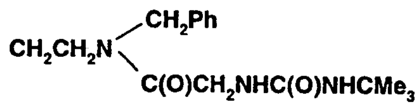
,

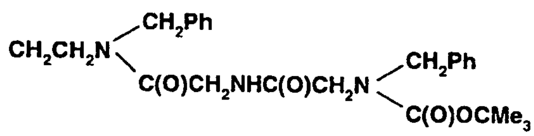
,

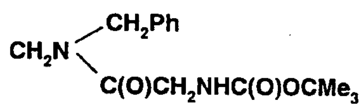
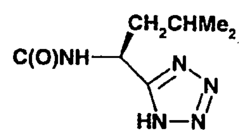
,

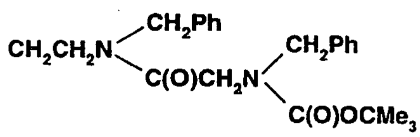
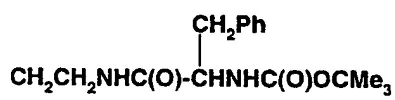
,

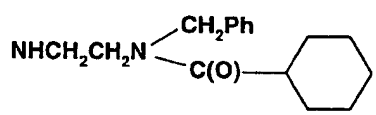
, ,

,

,

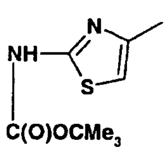
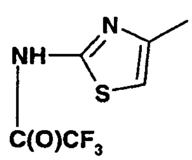
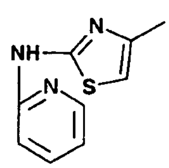
, ,

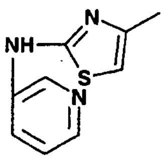
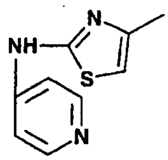
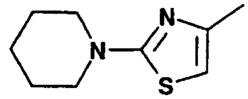
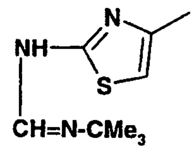
, ,

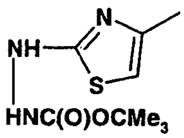
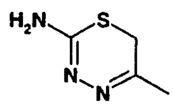
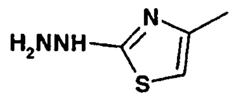
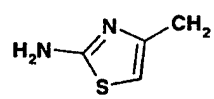
and ;

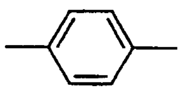
or

(iv) **X** is selected from the group consisting of:

H, , , ,

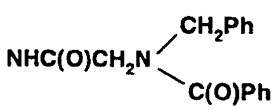
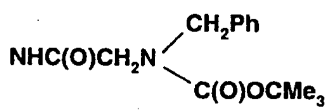
, , , ,

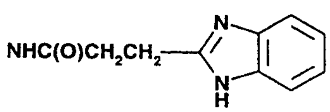
 ,  and ;

Aryl is ;

Y is absent; and

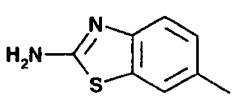
Z is selected from the group consisting of: NHC(O)NH-$CHPr_2$, $NHC(S)NBu_2$, $NHC(O)NBu_2$, $NHC(O)CH_2CH_2N(CH_2Ph)_2$,

, , and

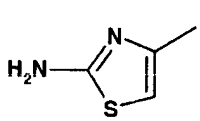
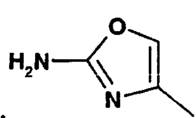
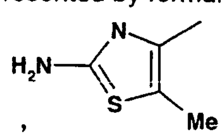
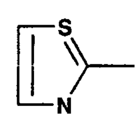
;

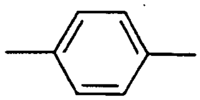
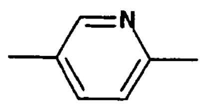
or

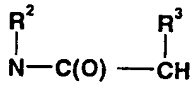
(v) **X** and **Aryl** together form **X'** which is defined as

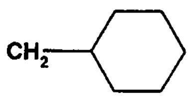
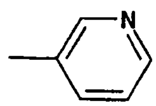
, and **Y** and **Z** are as defined in paragraph (i).

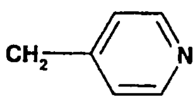
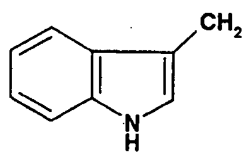
A preferred group of compounds is represented by formula 1 wherein **X** is

, ,  or ,

Aryl is  or  ,

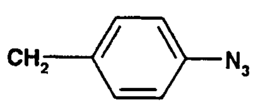
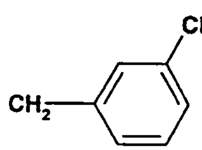
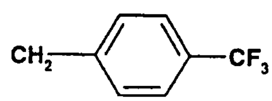
Y is  wherein $\mathbf{R^2}$ is hydrogen and $\mathbf{R^3}$ is H,

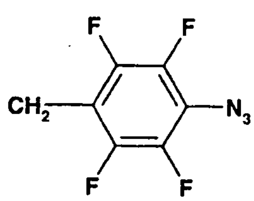
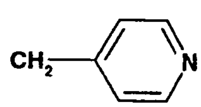
 , CH_2Ph,  ,

 or  , and

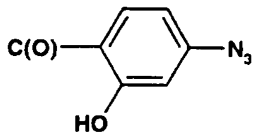
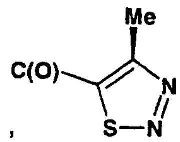
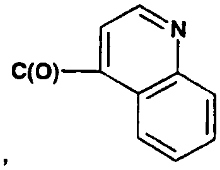
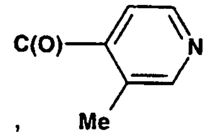
Z is NR^4R^5 wherein

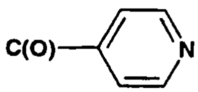
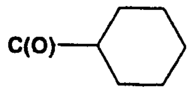
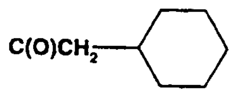
$\mathbf{R^4}$ is H, CH_2Ph,

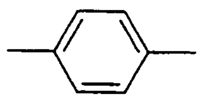
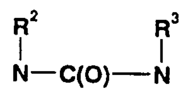
 ,  , 

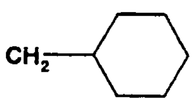
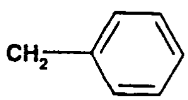
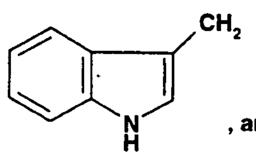
 or  , and

$\mathbf{R^5}$ is

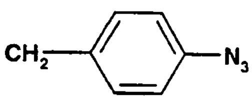
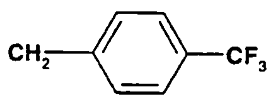
, , , ,

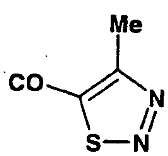
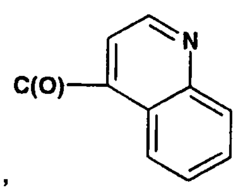
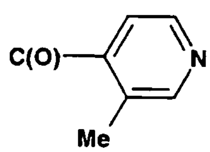
, , , C(O)Ph or C(O)CMe$_3$.

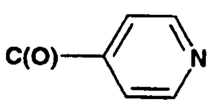
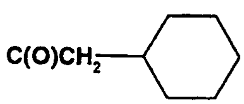
A more preferred group is represented by formula 1 wherein X is as defined in the last instance, **Aryl** is , Y is  wherein $\mathbf{R}^2$ is H and $\mathbf{R}^3$ is H,

,  or , and

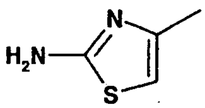
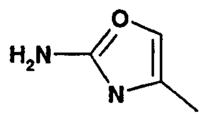
Z is NR^{4}R^5 wherein

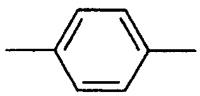
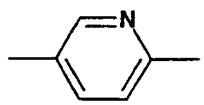
$\mathbf{R}^4$ is H, CH$_2$Ph,  or , and

$\mathbf{R}^5$ is , , ,

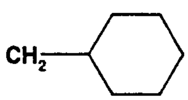
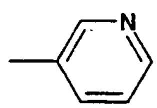
, , C(O)Ph or C(O)OCMe$_3$.

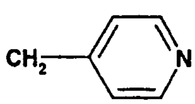
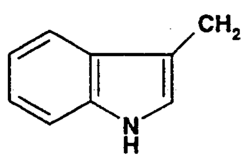
A most preferred group is represented by formula 1 wherein **X** is

 or ,

Aryl is  or ,

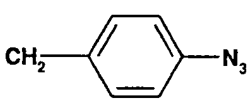
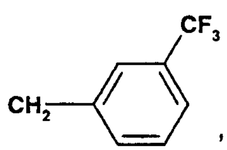
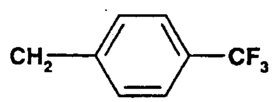
Y is $N(R^2)-C(O)-CH(R^3)$ wherein $\mathbf{R^2}$ is hydrogen and $\mathbf{R^3}$ is H,

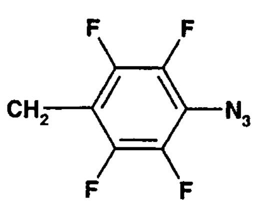
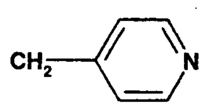
, CH_2Ph, ,

 or , and

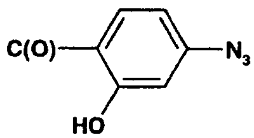
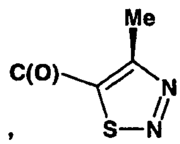
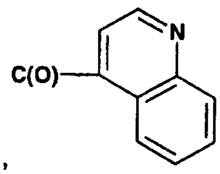
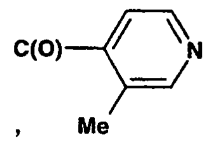
Z is NR^4R^5 wherein

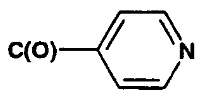
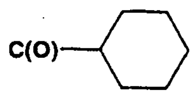
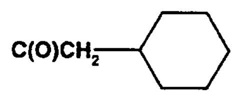
$\mathbf{R^4}$ is H, CH_2Ph,

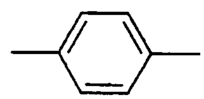
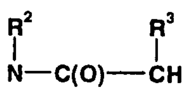
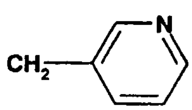
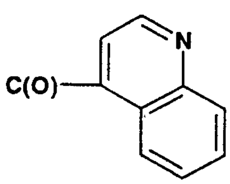
, , 

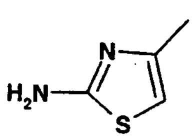
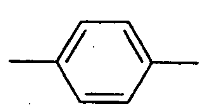
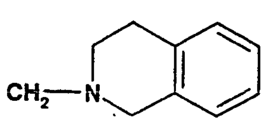
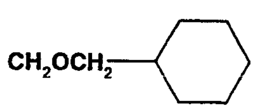
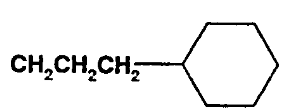
 or , and

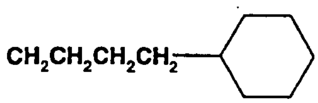
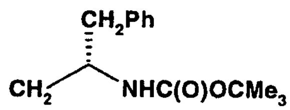
$\mathbf{R^5}$ is

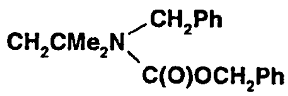
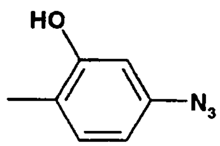
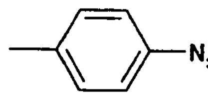
 ,  ,  ,  ,

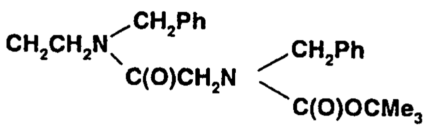
 ,  ,  , C(O)Ph or C(O)CMe_3 .

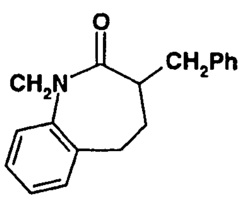
Still another most preferred group is represented by formula 1 wherein **X** is as defined in the last instance, **Aryl** is  , Y is  wherein $\mathbf{R}^2$ is H and $\mathbf{R}^3$ is H or  , and **Z** is NR^4R^5 wherein $\mathbf{R}^4$ is H or CH_2Ph, and $\mathbf{R}^5$ is  , C(O)Ph or C(O)$OCMe_3$.

Another preferred group of compounds is represented by formula 1 wherein **X** is  , **Aryl** is  , **Y** is NH-C(O) and **Z** is  ,  ,  ,

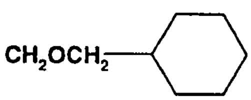
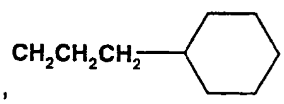
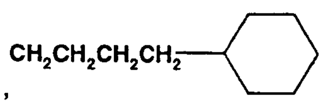
 ,  ,

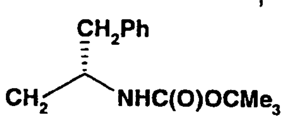
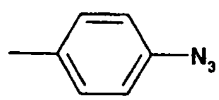
 ,  ,  ,

 or

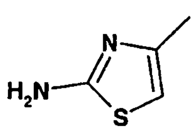
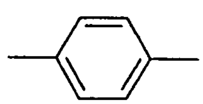


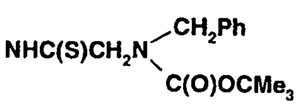
Another more preferred group is represented by formula 1 where X, Aryl and Y are as defined in the last instance and Z is

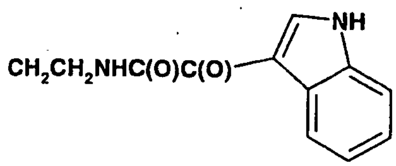
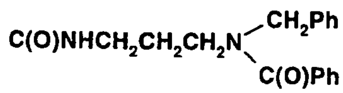
 ,  ,  ,

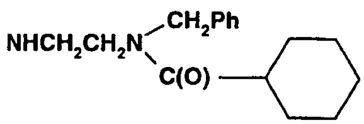
 or  .

Still another preferred group of compounds is represented by formula 1

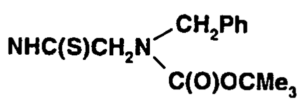
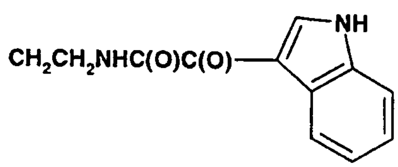
wherein X is  , Aryl is  and Z is

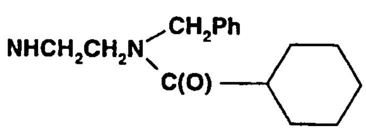
 ,

,  and

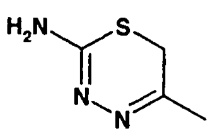
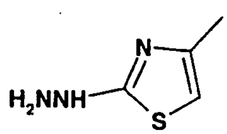
.

Still another more preferred group of compounds is represented by formula 1 wherein X, Aryl and Y are defined in the last instance and Z is

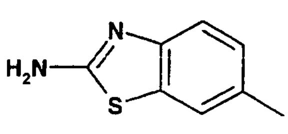
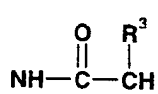
,  and

.

Yet another preferred group of compounds is represented by formula wherein X is

 or , Aryl and Y are as defined herebefore, and Z is $NHC(O)NBu_2$.

Again, another preferred group of compounds is represented by formula 1 wherein X and Aryl together form X^1 which is defined as

, Y is  wherein R^3 is H or $PhCH_2$, Y is

as defined hereinbefore and Z is NR^4R^5 wherein R^4 is H or CH_2Ph and R^5 is $C(O)OCMe_3$.

A further aspect of this invention is to provide compounds useful in the methods of this invention and for pharmaceutical compositions comprising those compounds.

Another aspect of this invention is to provide processes for preparing the compounds of this invention.

Still a further aspect of this invention is to provide pharmaceutical compositions containing the compounds of this invention and methods for treating herpes infection in a mammal using those pharmaceutical compositions.

Detailed Description of the Invention

As used herein, the following definitions apply unless otherwise noted:

With reference to the instances where *(R)* or *(S)* is used to designate the configuration of a radical, e.g. R^4 of the compound of formula 1, the designation is done in the context of the compound and not in the context of the radical alone.

The term "halo" as used herein means a halo radical selected from bromo, chloro, fluoro or iodo.

The term "herpes" as used herein refers to any virus in the herpes family of viruses and particularly, to those herpesviruses that encode a herpes helicase-primase homologous to the herpes helicase-primase of HSV-1. The herpes family of viruses includes, but is not limited to, HSV-1, HSV-2, cytomegalovirus, varicella zoster virus and Epstein-Barr virus.

The term "lower alkanoyl" as used herein, either alone or in combination with another radical, means a straight chain 1-oxoalkyl containing from one to six carbon atoms or a branched chain 1-oxoalkyl containing from four to six carbon atoms; for example, acetyl, propionyl(1-oxopropyl), 2-methyl-1-oxopropyl, 2-methylpropionyl and 2-ethylbutyryl. Note that the term "lower alkanoyl" when used in combination with "lower cycloalkyl" would include "(lower cycloalkyl)carbonyl".

The term "(1-3C)alkyl" as used herein, either alone or in combination with another radical, means alkyl radicals containing from one to three carbon atoms and includes methyl, ethyl, propyl and 1-methylethyl.

The term "lower alkyl" as used herein, either alone or in combination with another radical, means straight chain alkyl radicals containing one to four carbon atoms and branched chain alkyl radicals containing three to four carbon atoms and includes methyl, ethyl, propyl, butyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl and 2,2-dimethylpropyl.

The term "(1-8C)alkyl" as used herein means straight and branched chain alkyl radicals containing from one to eight carbon atoms and includes ethyl, butyl, 1-methylpropyl, 1-ethylpropyl, 2,2-dimethylpropyl, 1-ethylbutyl, 2-ethyl-2-methylbutyl, 2-ethylbutyl, 1-propylbutyl, 2-propylpentyl and the like.

The term "lower alkenyl" as used herein means an aliphatic hydrocarbon containing two to four carbon atoms and one double bond and includes ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl and 3-butenyl.

The term "lower alkynyl" as used herein means an aliphatic hydrocarbon containing two to four carbon atoms and one triple bond and includes ethynyl, 1-propynyl, 2-propynyl and 1-butynyl.

The term "{1-(lower alkyl)-(lower cycloalkyl)}" as used herein means a lower cycloalkyl radical bearing a lower alkyl substituent at position 1; for example, 1-ethylcyclopropyl, 1-propylcyclopentyl and 1-propylcyclohexyl.

The term "lower cycloalkyl" as used herein, either alone or in combination with another radical, means saturated cyclic hydrocarbon radicals containing from three to seven carbon atoms and includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "lower alkoxy" as used herein means straight chain alkoxy radicals containing one to four carbon atoms and branched chain alkoxy radicals containing three to four carbon atoms and includes methoxy, ethoxy, propoxy, 1-methylethoxy, butoxy and 1,1-dimethylethoxy. The latter radical is known commonly as *tert*-butoxy.

The term "amino" as used herein means an amino radical of formula $-NH_2$. The term "lower alkylamino" as used herein means alkylamino radicals containing one to six carbon atoms and includes methylamino, propylamino, (1-methylethyl)amino and (2-methylbutyl)amino. The term "di(lower alkyl)amino" means an amino radical having two lower alkyl substituents each of which contains one to six carbon atoms and includes dimethylamino, diethylamino, ethylmethylamino and the like.

The term "Het" as used herein means a monovalent radical derived by removal of a hydrogen from a five- or six-membered saturated or unsaturated heterocycle; said five-membered heterocycle containing from one to four nitrogen atoms (for example tetrazolyl), or said five- or six-membered heterocycle containing from one to three heteroatoms selected from nitrogen, oxygen and sulfur. Optionally, the heterocycle may bear one or two substituents; for example, *N*-oxido, lower alkyl, phenyl-(1-3C)alkyl, lower alkoxy, halo, amino or lower alkylamino. Examples of suitable heterocycles and optionally substituted heterocycles include pyrrolidine, tetrahydrofuran, thiazolidine, pyrrole, 1*H*-imidazole, 1-methyl-1*H*-imidazole, pyrazole, furan, thiophene, oxazole, isoxazole, thiazole, 2-methylthiazole, 2-aminothiazole, 2-(methylamino)-thiazole, piperidine, 1-methylpiperidine, 1-methylpiperazine, 1,4-dioxane, morpholine, pyridine, pyridine *N*-oxide, pyrimidine, 2,4-dihydroxypyrimidine and 2,4-dimethylpyrimidine.

The term "bicyclic heterocyclic system" as used herein, either alone or in combination with another radical, means a heterocycle as defined above fused to one or more other cycle be it a heterocycle or a lower cycloalkyl. Examples of suitable heterocyclic systems include: thiazolo[4,-b]pyridine, quinoline, or indole.

The term "pharmaceutically acceptable carrier" or "veterinarily acceptable carrier" as used herein means a non-toxic, generally inert vehicle for the active ingredient which does not adversely affect the ingredient.

The term "effective amount" means a predetermined antiviral amount of the antiviral agent, i.e. an amount of the agent sufficient to be effective against the virus *in vivo.*

The term "inhibit", when used in connection with enzymatic activity, refers generally to inhibiting the enzymatic activity by at least about 50% at a concentration of about 100 μM (and preferably at a concentration of about 50 μM, more preferably, at a concentration of about 25 μM, even more preferably, at a concentration of about 10 μM and most preferably, at a concentration of about 5 μM or less) in a conventional *in vitro* assay for enzymatic inhibition. In contrast, the term "inability to inhibit" refers generally to inhibiting enzymatic activity by no more than about 50% at concentration of about 100 μM. For example, a compound with an HSV-1 helicase-primase IC_{50} value of 1.5 μM inhibits HSV-1 helicase-primase activity by 50% at a concentration of 1.5 μM. Therefore, this compound is an HSV-1 helicase-primase inhibitor, as the term is used herein. However, a compound having an IC_{50} value of 150 μM inhibits enzymatic activity by 50% at a concentration of 150 μM and therefore, is not considered an inhibitor of that enzyme.

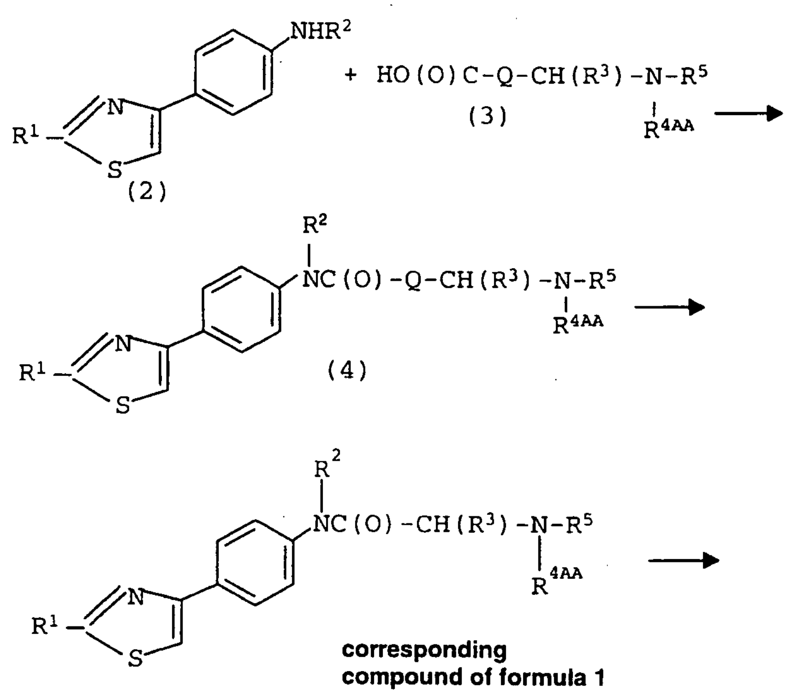
Processes for preparing the compounds

The compounds of this invention can be prepared by a variety of processes. Description of some such methods are found in standard textbooks such as

"Annual Reports In Organic Synthesis - 1994", P.M. Weintraub et al., Eds., Academic Press, Inc., San Diego, CA, USA, 1994 (and the preceding annual reports), "Vogel's Textbook of Practical Organic Chemistry", B.S. Furniss et al., Eds., Longman Group Limited, Essex, UK, 1986, and "Comprehensive Organic Synthesis", B.M. Trost and I. Fleming, Eds., Pergamon Press, Oxford, UK, 1991, Volumes 1 to 8.

One general process is represented by Scheme 1:

Scheme 1



wherein R^1, R^2, R^3 and R^5 are as defined herein, Q is absent (i.e. a valance bond) or methylene, and R^{4AA} is an amino protecting group or a radical as defined for R^4 hereinbefore other than hydrogen.

According to Scheme 1, a thiazolylaniline derivative of formula 2 is coupled with an amino acid derivative of formula 3 to give a corresponding

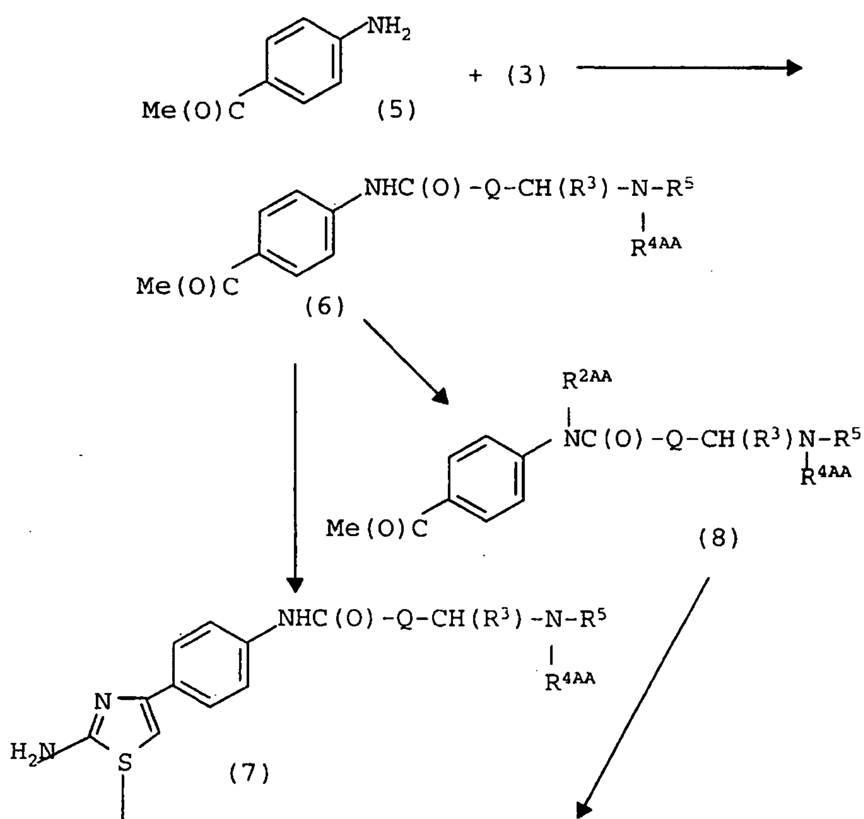
aminoamide of formula 4. In the instance where R^{4AA} has the same significance as R^4 but excluding hydrogen, then the aminoamide of formula 4 so obtained is a compound of formula 1. In the instance where R^{4AA} is an amino protecting group, the compound of formula 4 so obtained can be deprotected to give the corresponding compound of formula 1 in which R^4 is hydrogen. The latter product, albeit a compound of formula 1, can also serve as an intermediate for further elaboration by standard methods to yield compounds of formula 1 in which R^4 is other than hydrogen.

The coupling of the 4-thiazolylaniline derivative of formula 2 and the amino acid of formula 3 is effected by the classical dehydrative coupling of a free carboxyl of one reactant with the free amino group of the other reactant in the presence of coupling agent to form a linking amide bond. Description of such coupling agents are found in general textbooks on peptide chemistry; for example, M. Bodanszky, "Peptide Chemistry", 2nd rev ed, Springer-Verlag, Berlin, Germany, 1993. Examples of suitable coupling agents are *N,N'*-dicyclohexyl-carbodiimide, 1-hydroxybenzotriazole in the presence of *N,N'*-dicyclohexylcarbodiimide or *N*-ethyl-*N'*-{(3-dimethylamino)propyl}carbodiimide. A very practical and useful coupling agent is the commercially available (benzotriazol-1-yloxy)tri-(dimethylamino)phosphonium hexafluorophosphate, either by itself or in the presence of 1-hydroxybenzotriazole. Still another very practical and useful coupling agent is commercially available 2-(1H-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyl-uronium tetrafluoroborate.

The coupling reaction is conducted in an inert solvent, e.g. dichloromethane, dimethylformamide, tetrahydrofuran or acetonitrile. An excess of a tertiary amine, e.g. diisopropylethylamine or *N*-methylmorpholine, is added to maintain the reaction mixture at a pH of about eight. The reaction temperature usually ranges between 0° and 50 °C and the reaction time usually ranges between 15 minutes and 24 hours.

A practical and convenient variation of the preceding process (Scheme 1) can be practiced by replacing the 4-thiazolylaniline derivative 2 with 4'-aminoacetophenone. This process is illustrated by Scheme 2:

Scheme 2



Corresponding compound of formula 1(R^2=H)

Corresponding compound of formula 1(R^2=lower alkyl)

wherein R^{2AA} is lower alkyl and R^3, R^{4AA}, R^5 and Q are as defined hereinbefore.

In Scheme 2, the compound of formula 5, namely 4'-aminoacetophenone, is coupled with amino acid derivative of formula 3, noted hereinbefore, to give a corresponding terminal methyl ketone of formula 6.

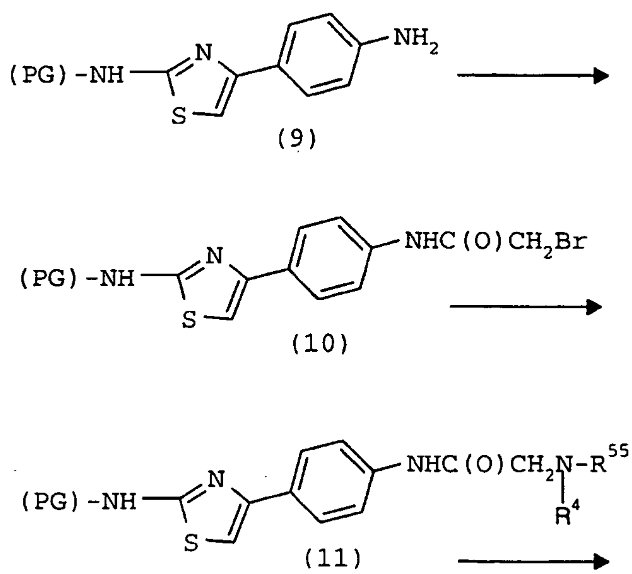
The methyl ketone 6 can be used to prepare corresponding compounds of formula 1 wherein R^2 is hydrogen as follows: The methyl ketone was reacted with thiourea and iodine according to the method of R.M. Dodson and L.C. King, J. Amer. Chem Soc. **1945**, *67*, 2242 to give the corresponding aminothiazole derivative of formula 7. In the instance where R^{4AA} has the same significance as R^4 but excluding hydrogen, then the aminothiazole derivative of formula 7 so obtained is a compound of formula 1. In the instance where R^{4AA} is an amino protecting group then the derivative of formula 7 so obtained can be deprotected to give a corresponding compound of Group 1-formula 1 wherein R^4 is hydrogen. If desired, the latter derivative can be converted by standard methods (e.g., *N*-alkylation, acylation, carbamate formation, etc.) with the appropriate agent to give corresponding compounds of formula 1 wherein R^4 is as defined hereinbefore other than hydrogen.

Alternately, the methyl ketone of formula 6 can be used to prepare compounds of formula 1 wherein R^2 is lower alkyl. Accordingly, the methyl ketone of formula 6 is subjected to *N*-alkylation with an appropriate lower alkyl bromide, chloride or iodide in the presence of a base to give the corresponding *N*-alkylated derivative of formula 8 wherein R^{2AA} is lower alkyl and Q, R^3, R^{4AA} and R^5 are as defined hereinbefore. The latter compound, when R^{4AA} is a radical as defined for R^4 of the compound of formula 1 other than hydrogen, can be transformed directly to the corresponding compound of formula 1, wherein R^1 is amino, R^2 is lower alkyl, R^4 is a radical other than hydrogen and Q, R^3 and R^5 are as defined hereinbefore. The transformation is effected by employing the previously noted method of Dodson and King for aminothiazole formation. On the other hand, the *N*-alkylated derivative of formula 8 wherein R^{4AA} is an amino protected group can be deprotected to give the corresponding

compounds of formula 1 wherein R^1 is amino, R^2 is lower alkyl, R^4 is hydrogen, and Q, R^3 and R^5 are as defined hereinbefore.

Still another variation is illustrated by Scheme 3:

Scheme 3



(R^1 is NH_2, R^2 and R^3 each is H, Q is absent, R^4 is as defined herein, and R^5 is R^{55} which is as defined herein for R^5 with the exception that it is not an acyl group)

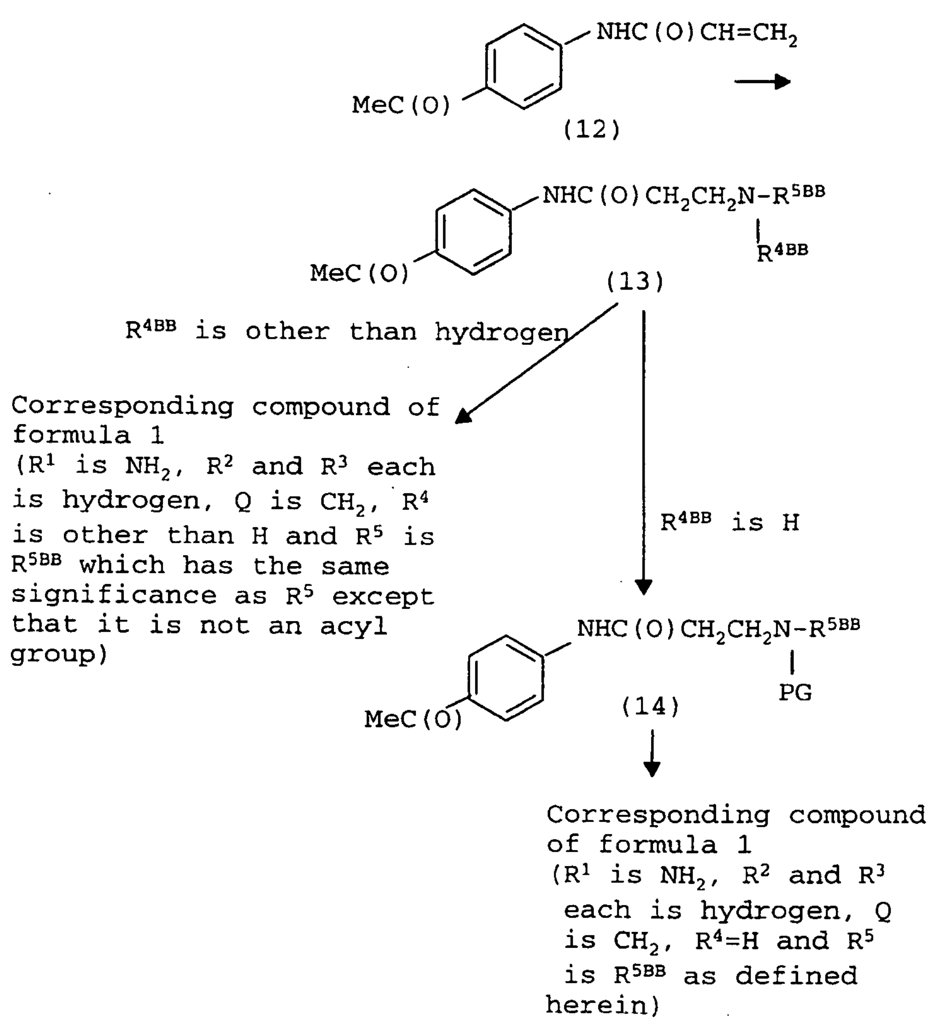
wherein PG is an amino protecting group, R^1 is amino, R^2 and R^3 each is hydrogen, Q is absent and R^4 and R^{55} are as defined hereinbefore.

According to Scheme 3, the protected aminothiazole derivative of formula 9 wherein PG represents an amino acid protecting group is reacted with bromoacetyl bromide to give the corresponding bromoacetamide 10. Displacement of the bromine of the latter compound with the appropriate primary or secondary amine gives the corresponding intermediate of formula 11. Removal of the protecting group PG from the latter intermediate gives

the corresponding compound of formula 1 wherein R^5 is R^{55} as defined hereinbefore.

Still another variation, which can be used for preparing compounds of formula 1 in which Q is methylene, is the process represented by Scheme 4:

Scheme 4



wherein R^1 is NH_2, R^2 and R^3 each is hydrogen, Q is methylene, R^{4BB} has the same significance as R^4 as described herein, R^{5BB} has the same significance as defined hereinbefore for R^5 with the exception it is not an acyl group, and PG is as amino protection group.

According to Scheme 4, *N*-(4-acetylphenyl)-2-propenamide is reacted with the appropriate primary or secondary amine to give the Michael adduct of formula 13 wherein R^{4BB} has the same significance as defined for R^4 hereinbefore, and R^{5BB} has the same significance as defined hereinbefore for R^5 with the exception that it is not an acyl group. Thereafter, the Michael adduct of formula 13 wherein R^{4BB} is other than hydrogen is transformed to corresponding compounds of formula 1 by the previously noted method of Dodson and King for aminothiazole formation. However, in the instance wherein R^{4BB} of the Michael adduct is hydrogen, the transformation to corresponding compounds of formula 1 proceeds with protecting the inherent secondary amine with an amino protecting group and the resulting amino protected derivative of formula 14 then is subjected to the Dodson and King method of aminothiazole formation, whereby the amino protecting group is cleaved *in situ* and the corresponding compound of formula 1 wherein R^4 is hydrogen is obtained. If desired, the compounds of formula 1 so obtained according to Scheme 4 can also serve as intermediates for elaboration to other compounds of formula 1 in which Q is methylene by conventional methods.

The amino acid derivative of formula 3, noted in Schemes 1 and 2, can be prepared readily by methods used in peptide chemistry. For example, the *N*-monosubstituted and *N,N*-disubstituted glycine derivatives of formula 3, wherein Q is absent, can be prepared by substituting the bromine of the appropriate ethyl bromoacetate with an appropriate primary or secondary amine in the presence of a tertiary amine for example, triethylamine or *N*-methylmorpholine, to obtain the corresponding α-aminoester having either a monosubstituted or disubstituted amino group. Subsequent hydrolysis with lithium hydroxide of the latter product (or an amino protected derivative thereof in the process involving the primary amine), gives the desired

protected *N*-monosubstituted, or the desired *N,N*-disubstituted amino acid derivative of formula 3 wherein Q is absent. Likewise, *N,N*-disubstituted β-amino acids of formula 3, wherein Q is methylene, can be prepared by a similar process wherein the ethyl bromoacetate derivative is replaced with the appropriate 3-bromopropionic ethyl ester derivative.

Examples of amino protective groups suitable for use in the above schemes include benzyloxycarbonyl, *tert*-butoxycarbonyl, 4-methoxybenzyloxycarbonyl or 2,2,2-trichloroethoxycarbonyl.

Other starting materials for the preceding processes are known or they can readily be prepared by standard methods from known starting materials. For example, 4′-aminoacetophenone (5) is available from the Aldrich Chemical Co., Milwaukee, WI, USA; and the requisite thiazolylaniline derivatives of formula 2 can be obtained by applying the classical thiazole preparation involving reacting the appropriate thioamide or thiourea of formula H_2N-C(S)-R^1 wherein R^1 is hydrogen, amino, lower alkylamino or di(lower alkyl)amino with 2-bromo-4′-nitroacetophenone (Aldrich Chemical Co.) according to method described by R.H. Wiley et al., Organic Reactions **1951**, *6*, 369-373 followed by reducing the intermediate product (with a nitro group) with iron powder in the presence of hydrochloric acid to obtain the desired thiazolylaniline derivative of formula 2 wherein R^1 is as defined in the last instance. Moreover, the preparation of *N*-(4-acetylphenyl)-2-propenamide (12) of Scheme 4 is described in example 3 herein; and the preparation of an example of the versatile starting material of formula 9 of Scheme 3 (wherein PG is *tert*-butoxycarbonyl) is given in example 2 herein.

Other useful starting materials are 3-(4-nitrophenyl)pyridine (M. Ishikura et al., Heterocycles **1984**, *22*, 265); 4-(4-aminophenyl)imidazole (I.E. Balaban and H. King, J. Chem. Soc., **1925**, *127*, 2711); and 2-(4-aminophenyl)thiazole (B.S. Friedman et al., J. Amer. Chem. Soc., **1937**, *59*, 2262). Similar starting materials which are aminophenyl substituted heterocycles are commercially available.

The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, the reaction can be successfully performed by conventional modification known to those skilled in the art, e.g. by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, or by modification illustrated in the examples herein.

Furthermore, if desired, the compound of formula 1 can be obtained in the form of a therapeutically acceptable acid addition salt. Such salts can be considered as biological equivalent of the compounds of formula 1. Examples of such salts are those formed with hydrochloric acid, sulfuric acid, phosphoric acid, formic acid, acetic acid or citric acid.

Antiherpes Activity

The antiviral activity of the compounds of formula 1 can be demonstrated by biochemical, microbiological and biological procedures showing the inhibitory effect of the compounds on the replication of herpes simplex viruses, types 1 and 2 (HSV-1 and HSV-2), cytomegalovirus, as well as acyclovir-resistant herpes simplex viruses and ganciclovir-resistant cytomegaloviruses.

A biochemical procedure for demonstrating antiherpes activity for compounds of formula 1 is described in the examples hereinafter. This particular assay is based on the evaluation of the ability of the test compound to inhibit HSV-1 helicase-primase, an essential enzyme for viral DNA replication.

Methods for demonstrating the inhibitory effect of the compounds of formula 1 on herpes viral replication involving *in vitro* and cell culture techniques are described in the examples.

The therapeutic effect of the compounds of formula 1 can be demonstrated in laboratory animals, for instance, the hairless mouse model for the topical treatment of cutaneous HSV-1 infections, P.H. Lee et al., International Journal of Pharmaceutics, **1993**, *93*, 139; the (HSV-2)-induced genitalis mouse model, R.W. Sidewell et al., Chemotherapy, **1990**, *36*, 58; and BALB/C mouse model infected with murine cytomegalovirus, D.L. Barnard et al., Antiviral Res., **1993**, *22*, 77, and J. Neyts et al., Journal of Medical Virology, **1992**, *37*, 67.

When a compound of formula 1, or one of its therapeutically acceptable acid addition salts, is employed as an antiviral agent, it is administered orally, topically or systemically to warm-blooded animals, e.g. humans, pigs or horses, in a vehicle comprising one or more pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice. For oral administration, the compound or a therapeutically acceptable salt thereof can be formulated in unit dosage forms such as capsules or tablets each containing a predetermined amount of the active ingredient, ranging from about 25 to 500 mg, in a pharmaceutically acceptable carrier. For topical administration, the compound can be formulated in pharmaceutically accepted vehicles containing 0.1 to 5 percent, preferably 0.5 to 5 percent, of the active agent. Such formulations can be in the form of a solution, cream or lotion.

For parenteral administration, the compound of formula 1 is administered by either intravenous, subcutaneous or intramuscular injection, in compositions with pharmaceutically acceptable vehicles or carriers. For administration by injection, it is preferred to use the compounds in solution in a sterile aqueous vehicle which may also contain other solutes such as buffers or

preservatives as well as sufficient quantities of pharmaceutically acceptable salts or of glucose to make the solution isotonic.

Suitable vehicles or carriers for the above noted formulations are described in standard pharmaceutical texts, e.g. in "Remington's The Science and Pratice of Pharmacy", 19th ed., Mack Publishing Company, Easton, Penn., 1995, or in "Pharmaceutical Dosage Forms And Drugs Delivery Systems", 6th ed., H.C. Ansel et al., Eds., Williams & Wilkins, Baltimore, Maryland, 1995.

The dosage of the compound will vary with the form of administration and the particular active agent chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small increments until the optimum effect under the circumstance is reached. In general, the compound of formula 1 is most desirably administered at a concentration level that will generally afford antivirally effective results without causing any harmful or deleterious side effects.

For oral administration, the compound or a therapeutically acceptable salt is administered in the range of 10 to 200 mg per kilogram of body weight per day, with a preferred range of 25 to 150 mg per kilogram.

With reference to topical application, the compound of formula 1 is administered topically in a suitable formulation to the infected area of the body e.g. the skin, the eye, the genitalia or part of the oral cavity, in an amount sufficient to cover the infected area. The treatment should be repeated, for example, every four to six hours until lesions heal.

For ocular administration, the compound of formula 1 is administered either topically or intraocularly (injection or implant) in a suitable preparation. For example, an implant containing the compound in a suitable formulation can be surgically placed in the posterior segment of the eye through a small incision.

With reference to systemic administration, the compound of formula 1 is administered at a dosage of 10 mg to 150 mg per kilogram of body weight per day, although the aforementioned variations will occur. However, a dosage level that is in the range of from about 10 mg to 100 mg per kilogram of body weight per day is most desirably employed in order to achieve effective results.

Although the formulations disclosed hereinabove are indicated to be effective and relatively safe medications for treating herpes viral infections, the possible concurrent administration of these formulations with other antiviral medications or agents to obtain beneficial results also included. Such other antiviral medications or agents include the antiviral nucleosides, for example, acyclovir, penciclovir, famciclovir, valacyclovir and ganciclovir, and antiviral surface active agents or antiviral interferons such as those disclosed by S.S. Asculai and F. Rapp in U.S. patent 4,507,281, March 26, 1985.

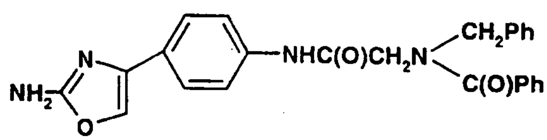
The following examples further illustrate and teach this invention. Temperatures are given in degrees Celsius. Solution percentages or ratios express a volume to volume relationship, unless stated otherwise. Nuclear magnetic resonance spectra were recorded on a Bruker 400 MHz spectrometer; the chemical shifts (δ) are reported in parts per million. The concentrations for the optical rotations are expressed in grams of the compound per 100 mL of solution. Abbreviations or symbols used in the examples include ATP: adenosine triphosphate; Boc: *tert*-butoxycarbonyl or 1,1-dimethylethoxycarbonyl; BOP: (benzotriazole-1-yloxy)tris-(dimethylamino)phosphonium hexafluorophosphate; Bu: butyl; DIPEA: diisopropylethylamine; DMAP: 4-(dimethylamino)pyridine; DMF: dimethylformamide; DMSO: dimethylsulphoxide; Et: ethyl; EtOAc: ethyl acetate; Et_2O: diethyl ether; Et_3N: triethylamine;EtOH: ethanol; MS (FAB) or FAB/MS: fast atom bombardment mass spectrometry; Hex: hexane; mAb: monoclonal antibody; Me: methyl; MeOH: methanol; PFU: plaque forming units; Ph: phenyl; Pr: propyl; TBTU: 2-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-

tetramethyluronium tetrafluoroborate; TFA: trifluoroacetic acid; THF: tetrahydrofuran.

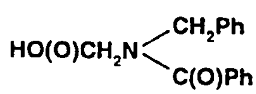
EXAMPLES

Example 1

N-{2-{{4-(2-amino-4-oxazolyl)phenyl}amino}-2-oxoethyl}-N-(benzyl)benzamide



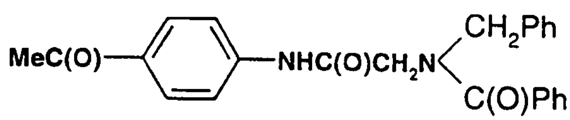
(a) 2-{(benzoyl)(benzyl)amino}acetic acid



To a mixture of benzylamine (54.6 mL, 0.5 mol) and triethylamine (140 mL, 1mol) in THF (1L) at 0° was added ethyl bromoacetate (83.5 g, 0.5 mol) over a 15 min period. The resulting mixture was stirred at 0° for an additional 15 min then at room temperature for 45 min after which time, the reaction was complete as indicated by TLC. The mixture was then cooled to 0° and benzoyl chloride (58 mL, 0.5 mol) was added over a 30 min period. Thereafter, the mixture was allowed to come to room temperature while being stirred for an additional 30 min. The reaction was complete (TLC). The reaction mixture was then added to a solution of $LiOH.H_2O$ (83.92 g, 2 mol) in H_2O (500 mL) followed the addition of MeOH (500 mL). After stirring at room temperature for 16h, 10 mL of aqueous 10N NaOH was added to the mixture, and the mixture was gently heated at reflux for 3h. Thereafter, THF and MeOH were removed under reduced pressure and the resulting

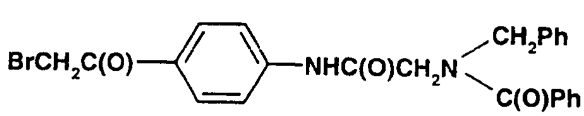
solution was diluted with H_2O to 2L. This solution was washed with EtOAc, acidified to pH 3 with concentrated aqueous HCl, and then extracted with EtOAc. The organic solution was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to afford 108.4 g of the desired acid as a white solid. MS (FAB) 270 $(MH)^+$. ^1H NMR (400 MHz, DMSO) 10.37 (broad s,1H), 7.22-7.44 (m, 10 H), 4.67, 4.51 (2 s, 2 H, 1:1 mixture of 2 rotamers), 3.98, 3.82 (2 s, 2H, 2 rotamers).

b) N-{2-{(4-acetylphenyl)amino}-2-oxoethyl}-N-(benzyl)benzamide



To a solution of 4'-aminoacetophenone (5.27 g, 38.98 mmol) in DMF (100 mL) was added 2-{(benzyl)-(benzoyl)amino}acetic acid (10 g, 37.13 mmol), BOP reagent (17.24 g, 38.98 mmol) and DIPEA (19.4 mL, 111.4 mmol). The resulting mixture was stirred for 16 h at room temperature. The resulting solution was diluted with EtOAc (1L), washed with H_2O (2 x 500 mL), aqueous 1N HCl (2 x 250 mL), H_2O (100 mL), saturated aqueous $NaHCO_3$ (2 x 220 mL) and brine (200 mL). The organic solution was dried ($MgSO_4$) and concentrated to afford 10.2 g of a light orange foam which was purified by trituration with EtOAc-hexane (1:2) to afford 8.3 g of the desired acetamide intermediate as a white solid. MS (FAB) 287 $(MH)^+$. ^1H NMR (400 MHz, DMSO) 10.18, 10.36 (2 s, 1H, 1:1 mixture of 2 rotamers), 7.90-7.94 (m, 2 H), 7.62, 7.72 (2 d, J = 8.4 Hz, 1H, 2 rotamers), 7.25-7.45 (m, 10 H), 4.56, 4.70 (2 s, 2 H, 2 rotamers), 3.98, 4.16 (2 s, 2 H, 2 rotamers).

c) N-(benzyl)-N-{{{4-(2-bromoacetyl)phenyl}amino}-2-oxoethyl}benzamide



Phenyl trimethylammoniumtribromide (3.52 g, 4.37 mmol) was added portion wise to a stirred solution of N-{2-{(4-acetylphenyl)amino}-2-oxoethyl}-N-(benzyl)benzamide (2.5 g, 6.46 mmol) in THF (150 mL) at room temperature. The resulting mixture was then stirred for 2h. The reaction was stopped by the addition of EtOAc (300 mL). The resulting solution was washed with aqueous 1N HCl, H_2O, saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated to afford 3.72 g of the desired bromoketone as a light yellow solid. MS(FAB) 467 $(MH)^+$. ^1H NMR (400 MHz, DMSO) 10.25, 10.46 (2 s, 1 H, 1:1 mixture of 2 rotamers), 7.96 (t, J = 8.9 Hz, 2H), 7.65, 7.75 (2 d, J = 8.7 Hz, 2 H), 7.26-7.45 (m, 10 H), 4.84, 4.85 (2 s, 2 H, 2 rotamers), 4.57, 4.71 (2 s, 2 H, 2 rotamers), 3.99, 4.18 (2 s, 2 H, 2 rotamers).

d) N-{2-{{4-(2-amino-4-oxazolyl)phenyl}amino}-2-oxoethyl}-N-(benzyl)benzamide

To a solution of N-(benzyl)-N-{{{4-(2-bromoacetyl)phenyl}amino}-2-oxoethyl}benzamide (3.0 g, 6.46 mmol) in DMF (60 mL) was added urea (1.93 g, 32.9 mmol). The resulting mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with EtOAc (250 mL). The resulting organic solution was washed with saturated aqueous $NaHCO_3$, H_2O (3 x 100 mL), brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude product was purified by two successive flash column chromatography operations using 2:1 EtOAc-hexane, then 20:1 $CHCl_3$-EtOH to afford 94 mg of the title compound. MS(FAB) 427 $(MH)^+$. ^1H NMR (400 MHz, DMSO) 9.90, 10.04 (2 s, 1 H, 1:1 mixture of 2 rotamers), 7.77 (s, 1H), 7.31-7.57 (m, 14 H), 6.65 (s, 2 H), 4.56, 4.65 (2 s, 2 H, 2 rotamers), 3.93, 4.12 (2 s, 2H, 2 rotamers).

Example 2

tert-Butyl *N*-{4-(4-Aminophenyl)-2-thiazolyl}-carbamate (a versatile starting

material of Scheme 3)

2,2,2-Trichloroethyl *N*-{4-(2-amino-4-thiazolyl)-phenyl}carbamate: 2,2,2-Trichloroethyl chloroformate (72.3 mL, 0.52 mol) was added (5 min) to an ice cold suspension of 4'-aminoacetophenone (67.6 g, 0.50 mol) and pyridine (50.5 mL, 0.62 mol). The reaction mixture was stirred at 0° for 15 min and then at room temperature (20-22°) for 45 min. The solvent was removed under reduced pressure. Et_2O (500 mL) and 1N aqueous HCl (500 mL) were added to the residue. The resulting solid was collected by filtration, washed with H_2O (1 L) and Et_2O (1 L), and dried over P_2O_5 in a desiccator under reduced pressure for 15 h to yield the expected carbamate (137.8 g, 89% yield). A mixture of the crude carbamate (137.8 g, 0.44 mol), thiourea (135.0 g, 1.77 mol) and I_2 (202.6 g, 0.80 mol) in isopropanol (670 mL) was heated at reflux for 18 h. The reaction mixture was cooled to room temperature and EtOAc (1 L) was added. The solution was successively washed with H_2O (2 x 600 mL), saturated aqueous $NaHCO_3$ (2 x 1 L) and then H_2O (2 x 1 L). A mixture of the organic layer and saturated aqueous 4N HCl (750 mL) was stirred vigorously at room temperature for 1.5 h. Et_2O (~800 mL) and H_2O (~300 mL) were added to the mixture to facilitate stirring. The suspension was filtered and the solid was washed with a 1:1 mixture of EtOAc and Et_2O (2 L). The solid was suspended in 20% aqueous NaOH (1.2 L). The mixture was extracted with EtOAc. The EtOAc extract was washed with brine (700 mL), dried ($MgSO_4$) and concentrated under reduced pressure to yield 2,2,2-trichloroethyl *N*-{4-(2-amino-4-thiazolyl)phenyl}carbamate (117.7 g, 75% yield) as a pale yellow solid: ^1H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 7.74 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 7.01 (s, 2H) 6.88 (s, 1H), 4.95 (s, 2H); MS (FAB) *m/z* 366/368/370/372 $(MH)^+$.

Example 3

N-(4-Acetylphenyl)-2-propenamide (a versatile starting material of Scheme 4)

A solution of acryloyl chloride (29.5 mL, 363 mmol) in CH_2Cl_2 (50 mL) was added dropwise (30 min) to an ice-cold solution of 4'-aminoacetophenone (49.0 g, 363 mmol) and Et_3N (50.6 mL, 363 mmol) in CH_2Cl_2 (300 mL). The reaction mixture was stirred at 0° for 15 min and then was concentrated under reduced pressure. The residue was dissolved with EtOAc. The solution was washed successively with 10% aqueous HCl, saturated aqueous $NaHCO_3$ and H_2O. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to afford the desired *N*-(4-acetylphenyl)-2-propenamide (52 g, 76% yield) as a yellow solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (broad s, 1H), 7.93 (d, J = 8.9 Hz, 2H), 7.72 (d, J = 8.9 Hz, 2H), 6.47 (dd, J = 1.0, 16.9 Hz, 1H), 6.33 (dd, J = 10.2, 16.9 Hz, 1H), 5.80 (dd, J = 1.0, 10.2 Hz, 1H), 2.58 (s, 3H); MS (FAB) *m/z* 190 $(MH)^+$.

Example 4

The following four assays (A, B and Ci and Cii) were used to evaluate antiherpes activity, and a fifth assay (D) was used to measure the stabilization of the DNA-herpes helicase-primase interaction.

A) HSV-1 DNA-Dependent ATP Assay (an *in vitro* assay based on the inhibition of HSV-1 helicase-primase).

a) Preparation of enzyme: HSV-1 helicase-primase holoenzyme was produced in triply infected Sf21 cells using recombinant baculoviruses expressing the UL5, UL8 and UL52 helicase-primase subunits, as described by S. Dracheva et al., J. Biol. Chem. **1995**, *270*, 14148. The crude enzyme was purified by ammonium sulfate precipitation, Source 15Q® chromatography and Sephacryl® S-300 HR gel filtration (both purification systems can be obtained from Pharmacia Biotech Inc., Montreal, Quebec, Canada), see S. Dracheva et al., *supra*.

b) Assay: The DNA-dependent ATPase assay, described by J.J. Crute et al., Nucleic Acids Res. **1988**, *16*, 6585, was modified and used to evaluate the capability of the compounds of formula 1 to inhibit HSV-1 helicase-primase activity. The reaction mixtures (80 μL each) contained 40 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES, pH 7.5), 10% (*v/v*) glycerol, 5.5 mM $MgCl_2$, 1 mM DL-dithiothreitol (DTT), 50 μg/mL acetylated bovine serum albumin, 3.3% (*v/v*) DMSO, 4 mM ATP, 25 μM single-stranded M13 DNA hybridized to double-tailed 68-mer oligonucleotide and 3 μg/mL HSV-1 helicase-primase. After incubation for 20 min at 34°, formation of inorganic phosphate from hydrolysis of ATP was monitored spectrophotometrically at 650 nm using acidic ammonium molybdate/malachite green reagent, P.A. Lanzetta et al., Anal. Biochem. **1979**, *100*, 95. DNA-dependent ATPase activity was calculated from the net absorbance change in the presence and absence of inhibition.

B) Inhibition of Herpes Simplex Virus (HSV-1) Replication in Cell Culture

Assay: BHK-21 cells clone 13 (ATCC CCL10) were incubated for two days in 850 cm^2 roller bottles ($2x10^7$ cells/bottle) with α-MEM medium (Gibco Canada Inc., Burlington, Ontario, Canada) supplemented with 8% (*v/v*) fetal bovine serum (FBS, Gibco Canada, Inc.). The cells were trypsinized and then 3,000 cells in 100 μL of fresh medium were transferred into each well of a 96-well microtiter plate. The cells were incubated at 37° for a period of 3 days to reach a density of 50,000 cells per well. The cells were washed twice with 100 μL of α-MEM supplemented with 2% heat inactivated FBS and incubated for 1-2 hours in 100 μL of the same medium.

Thereafter, the cells were infected with HSV-1 strain F or KOS (multiplicity of infection = 0.05 PFU/cell) in 50 μL of α-MEM supplemented with 2% heat inactivated FBS. Following one hour of virus absorption at 37°, the medium was removed and the cells were washed with α-MEM supplemented with 2% heat inactivated FBS (2 x 100 μL). The cells were incubated with or without 100 μL of the appropriate concentration of test reagent in α-MEM medium supplemented with 2% heat inactivated FBS. After 24 hours of incubation at

37°, the extent of viral replication was determined by an ELISA assay; for instance, the following assay that detects the late glycoprotein C of HSV-1.

Cells were fixed in the microtiter plate with 100 μL of 0.063% glutaraldehyde in phosphate buffered saline for 30 min at room temperature. The microtiter plate was then washed once with casein blocking solution and blocked with 200 μL of the same solution for one hour at room temperature. Thereafter, 100 μL of mAb C11 recognizing the glycoprotein C of HSV-1 (see E. Trybala et al., Journal of General Virology, **1994**, *75*, 743) was added to each well for two hours at room temperature. The plate was washed three times with phosphate buffered saline containing 0.05% polyoxyethylene (20) sorbitan monooleate. The cells were incubated with 100 μL of sheep anti-mouse IgG horseradish peroxidase for one hour at room temperature in the dark.

The plate was washed three times with 200 μL of the above-noted phosphate buffer saline preparation, and then once with 0.1 M sodium citrate (pH 4.5). Thereafter, 100 μL of orthophenylenediamine dihydrochloride (OPD, Gibco, Canada Inc.) was added to each well. The plate was agitated on a microplate shaker for 30 min in the dark. Color development was monitored at 450 nm using a microplate spectrophotometer.

SAS was used to calculate % inhibition of viral replication and to generate EC_{50} values.

C) Inhibition of Human Cytomegalovirus (HCMV) replication

The effect of compounds on the replication of HCMV has been measured by using an ELISA-based assay (ELISA) and a plaque reduction assay (PRA).

Ci) ELISA ASSAY:

Hs-68 cells (ATCC # CRL 1635) were seeded in 96 well microtiter plates at 10,000 cells/well in 100 μL of DMEM medium (Gibco Canada Inc.)

supplemented with 10% fetal bovine serum (FBS, Gibco Canada Inc.). The plates were incubated for 3 days at 37° to allow the cells to reach 80-90% confluency prior to the assay.

The medium was removed from wells by aspiration. The cells then were infected at a multiplicity of infection (MOI) of 0.01 PFU/cell with 50 μL of HCMV (strain AD169, ATCC VR-538) in DMEM medium supplemented with 5% heat inactivated FBS (assay medium). The virus was allowed to adsorb to cells for 2 h at 37°. Following viral adsorption, the medium was removed from the wells by aspiration. The cells were washed twice with 200 μL of assay medium to remove unabsorbed virus. The cells were then incubated with or without 100 μL of appropriate concentrations of test reagent in assay medium. After 8 days of incubation at 37°, the extent of viral replication was determined by an ELISA assay which detects the late structural protein p28 of HCMV.

Eight days after infection, the medium was aspirated from the wells. Non-specific binding sites were blocked by adding 200 μL of phosphate buffered saline containing 1% (*w/v*) bovine serum albumin (blocking buffer) to each well and incubating the plates for 30 min at room temperature. After removal of the blocking buffer by aspiration, the cells were fixed with 100 μL of cold ethanol-acetone solution (95:5) per well. The plates were placed at –20° for 30 min. The plates were washed 4 times with phosphate buffered saline containing 0.05% (*v/v*) polyoxyethylene sorbitan monolaurate (Tween 20®). Thereafter, 100 μL of mAb UL99 (Advanced Biotechnologies Inc., # 13-130-100) recognizing HCMV protein p28 was added to each wells and plates were incubated for 2 h at room temperature. The plates were washed four times with 200 μL of the above-noted phosphate buffered saline/Tween-20® solution. The cells were then incubated with 100 μL of sheep anti-mouse IgGγ horseradish peroxidase conjugated for 2 h at room temperature. The plates were then washed four times with 200 μL of above-noted phosphate buffered saline/Tween-20® solution. Thereafter, 100 μL of ortho phenylenediamine dihydrochloride (OPD, Gibco Canada Inc.) solution was added to each well and the plates were agitated on a microplate shaker

for 30 min in the dark. Color development was monitored at 450 nm using a microplate spectrophotometer.

The SAS program was used to calculate the % inhibition of viral replication and to generate EC_{50} values.

The EC_{50} values obtained according to this assay method for certain thiazolylphenyl derivatives of this invention are listed in the following tables under the heading ELISA CMV.

Cii) PRA ASSAY:

Hs-68 cells (ATCC # CRL 1635) were seeded in 12-well plates at 83,000 cells/well in 1 mL of DMEM medium (Gibco Canada Inc.) supplemented with 10% fetal bovine serum (FBS, Gibco Canada Inc.). The plates were incubated for 3 days at 37° to allow the cells to reach 80-90% confluency prior to the assay.

The medium was removed from the cells by aspiration. The cells were then infected with approximately 50 PFU of HCMV (strain AD169, ATCC VR-538) in DMEM medium supplemented with 5% inactivated FBS (assay medium). The virus was allowed to adsorb to cells for 2 h at 37°. Following viral adsorption, the medium was removed from the wells by aspiration. The cells were then incubated with or without 1 mL of appropriate concentrations of test reagent in assay medium. After 4 days of incubation at 37°, the medium was exchanged with fresh medium containing test compound and 4 days later the cells were fixed with 1% aqueous formaldehyde and stained with a 2% crystal violet solution in 20% ethanol in water. Microscopic plaques were counted using a stereomicroscope. Drug effects were calculated as a percent reduction in the number of plaques in the presence of each drug concentration compared to the number observed in the absence of drug. Ganciclovir was used as a positive control in all experiments.

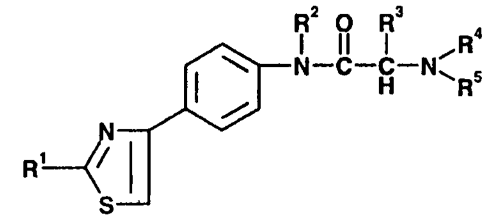
The EC_{50} values obtained according to this assay for certain thiazolyl derivatives of this invention are listed in the following tables under the heading PRA CMV.

Example 5

In conjunction with the appropriate starting materials and intermediates, the aforementioned procedures can be used to prepare other compounds of this invention. Examples of compounds thus prepared are listed in Tables 1 to 7, together with mass spectrum data for the individual compounds and the results obtained from three assays demonstrating antiherpes activity.

TABLE 1

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H, R^3 is H, and R^4 and R^5 are designated as follows:

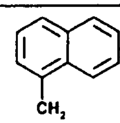
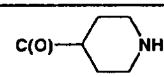
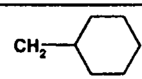
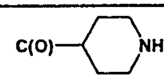
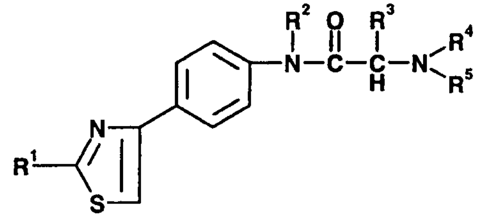
Entry No.	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
101	H		79	1.5		>11	389
102	CH_2Ph		>50	32	>59		450
103			>50	5.5	2.2	38	456

TABLE 1

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H, R^3 is H, and R^4 and R^5 are designated as follows:

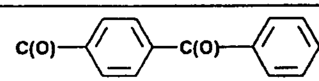
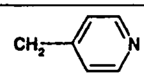
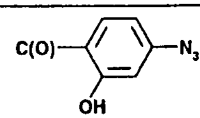
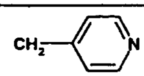
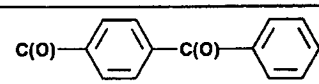
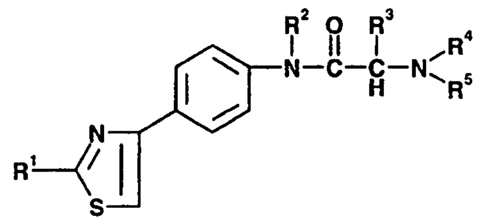
Entry No.	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
104	CH_2Ph		>2				547
105			0.66				501
106			8.9				548

TABLE 1

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H, R^3 is H, and R^4 and R^5 are designated as follows:

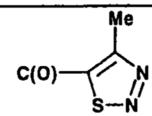
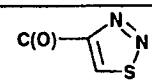
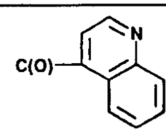
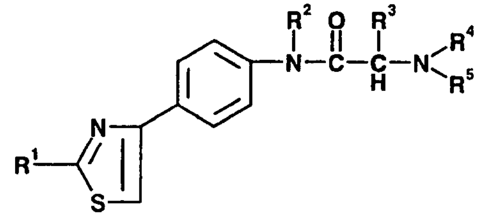
Entry No.	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
107	CH_2Ph		0.15	0.01			465
108	CH_2Ph		2.1	0.46			451
109	CH_2Ph		0.12	0.037			494

TABLE 1

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H, R^3 is H, and R^4 and R^5 are designated as follows:

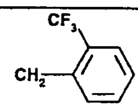
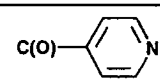
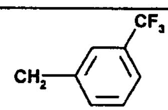
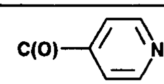
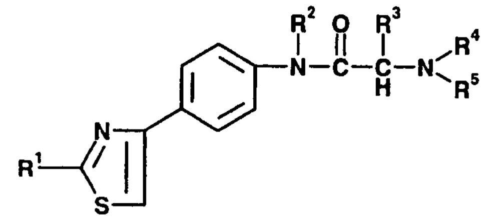
Entry No.	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
110			3.4	0.55			512
111			0.69	0.15			512
112	CH_2Ph	$C(O)(CH_2)_5NH_2$	90				680

TABLE 1

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H, R^3 is H, and R^4 and R^5 are designated as follows:

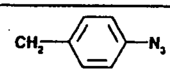
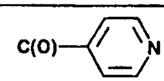
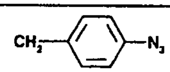
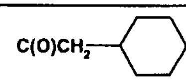
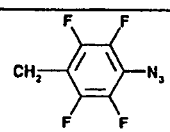
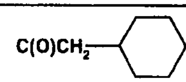
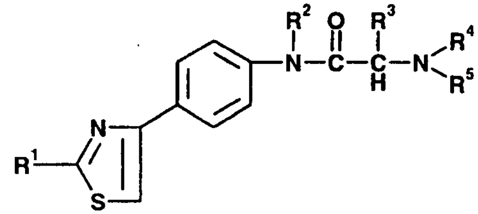
Entry No.	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (m/z) $(MH)^+$
113			0.52				485
114			0.082				504
115			1.0			15	576

TABLE 1

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H, R^3 is H, and R^4 and R^5 are designated as follows:

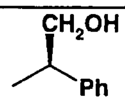
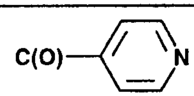
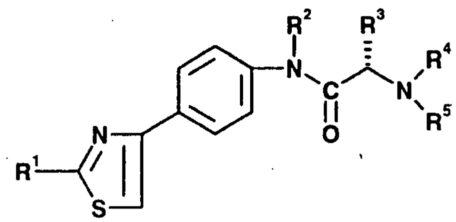
Entry No.	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (m/z) $(MH)^+$
116	CH_2Ph	$CH_2C(O)N(Me)CH_2Ph$	1.2			8.5	500
117	CH_2Ph	$CH_2C(O)NHCH_2Ph$	1.2			13	486
118	CH_2Ph	$C(O)CH_2OH$				11	397
119			57	0.24			474

TABLE 2

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H, and R^3, R^4 and R^5 are designated as follows:

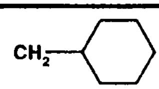
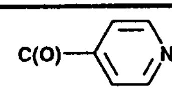
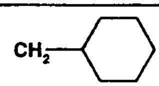
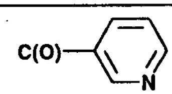
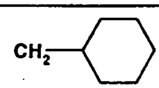
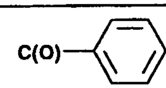
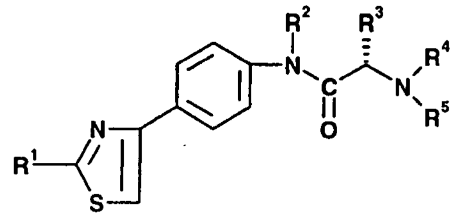
Entry No.	R^3	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
201		H		0.71	0.091			450
202		H		1.6	0.25			450
203		H		0.58	0.81			449

TABLE 2

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H, and R^3, R^4 and R^5 are designated as follows:

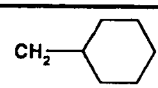
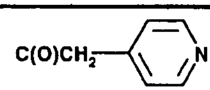
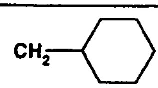
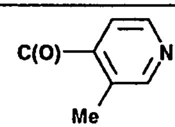
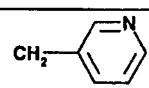
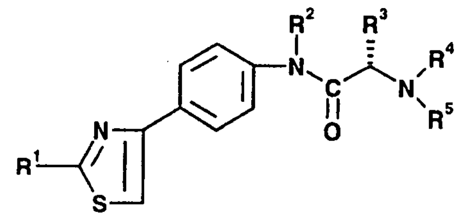
Entry No.	R^3	R^4	R^5	HSV-1 IC_{50} μM	HSV-1 EC_{50} μM	ELISA CMV EC_{50} μM	PRA CMV EC_{50} μM	FAB/MS (*m/z*) $(MH)^+$
204		H		3.4	1.2			464
205		H		0.48	0.30			464
206		H	$C(O)OCMe_3$	0.13	0.043	20		440

TABLE 2

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H, and R^3, R^4 and R^5 are designated as follows:

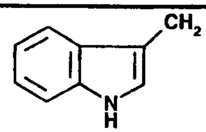
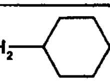
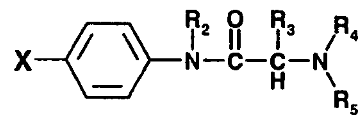
Entry No.	R^3	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
207		H	$C(O)OCMe_3$	0.095			18	478
208	Entry 208 is the enantiomer at R^3 of Entry 207			1.7			>16	478
209	$(CH_2)_4NH_2$	CH_2Ph	$C(O)CH_2$ 	2.5			7.2	534

TABLE 3

Compound of formula 1 having the structure



wherein R^2 and R^3 each is hydrogen and X, R^4 and R^5 are designated as follows:

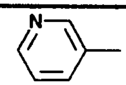
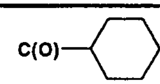
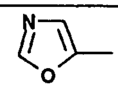
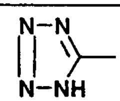
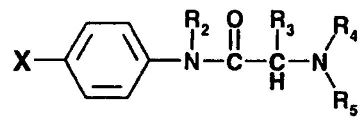
Entry No.	X	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
301		CH_2Ph		6.6	2.5	27		428
302		CH_2Ph	C(O)Ph	>50	>16	45		412
303	$NH_2S(O)_2$—	CH_2Ph	C(O)Ph	33	>51	16		424
304		CH_2Ph	C(O)Ph	>50	>48	62		413

TABLE 3

Compound of formula 1 having the structure



wherein R^2 and R^3 each is hydrogen and X, R^4 and R^5 are designated as follows:

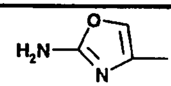
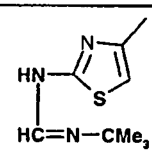
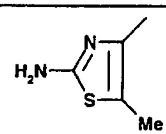
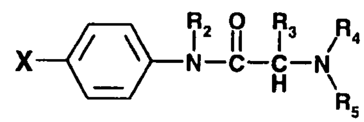
Entry No.	X	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
305		CH_2Ph	C(O)Ph	0.38	0.054	41		427
306	$H_2NC(O)NHCHMe$-	CH_2Ph	C(O)Ph	>50	>38	89		431
307		H	$PhCH_2$	>50	11	36		422
308		CH_2Ph	C(O)Ph	0.14	0.42	25		457

TABLE 3

Compound of formula 1 having the structure



wherein R^2 and R^3 each is hydrogen and X, R^4 and R^5 are designated as follows:

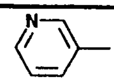
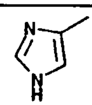
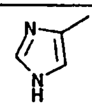
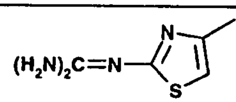
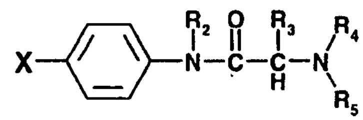
Entry No.	X	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
309		H	CH_2Ph	>50	63	>70		318
310		CH_2Ph	$C(O)OCMe_3$	40	6.8	67		407
311		CH_2Ph	C(O)Ph	>50	7.9	25		411
312		CH_2Ph	C(O)Ph	45			>4	485

TABLE 3

Compound of formula 1 having the structure



wherein R^2 and R^3 each is hydrogen and X, R^4 and R^5 are designated as follows:

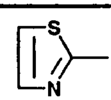
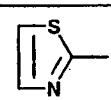
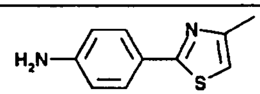
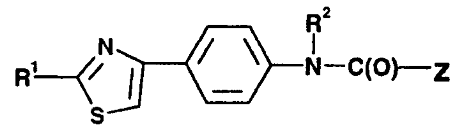
Entry No.	X	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
313		CH_2Ph	C(O)Ph	0.63			22	428
314		CH_2Ph	C(O)OCMe$_3$	0.24			13	424
315		CH_2Ph	C(O)OCMe$_3$	>50			3.5	515

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

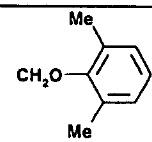
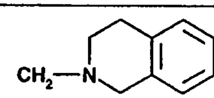
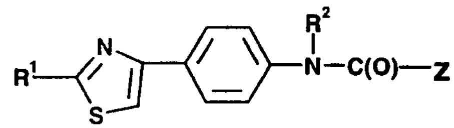
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
401	CH_2OCH_2Ph	7.4	>15	1.5		430
402	CH_2OPh	35	>20	2.8		326
403		3.2	4.0	1.6	23	354
404		0.63	11	12		365
405	OCH_2CHMe_2	28	14		12	292

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

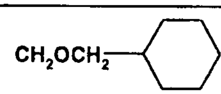
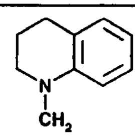
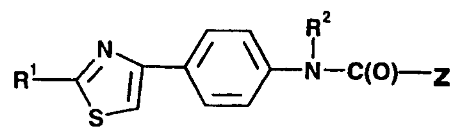
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
406	CH_2CH_2Ph	3.9	1.5		22	324
407		0.44	18	20		346
408		4.9	1.3	4.0		365
409	$CH_2CH_2CH_2Ph$	1.7	>1.0			338
410	CH_2SCH_2Ph	2	>8	12		356
411	CH=CHPh	3.8	0.75	5.6		222

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

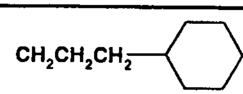
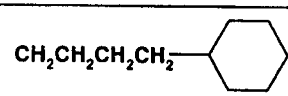
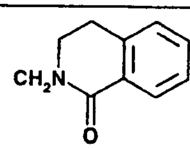
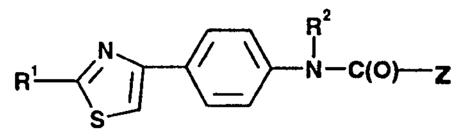
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
412		0.41	2.0	7.0		344
413		0.14	11	>39		358
414		4.4	0.91	1.6	50	379

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

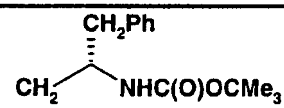
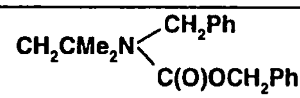
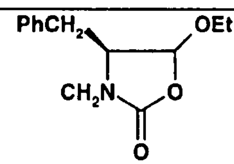
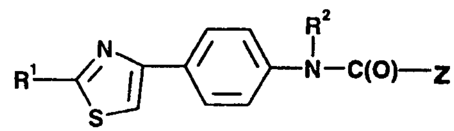
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
415		2	0.73	0.85	>6	453
416		0.62	0.86	4.5	>8.5	515
417		2.6	1.5	>12		453

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

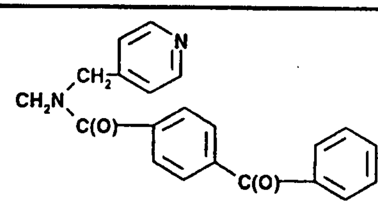
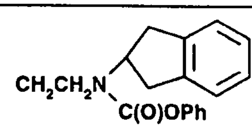
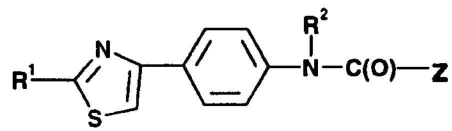
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (m/z) $(MH)^+$
418		9.0				548
419					14	499

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

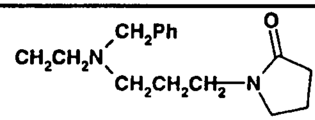
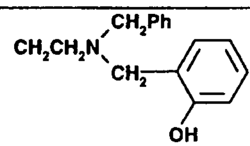
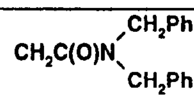
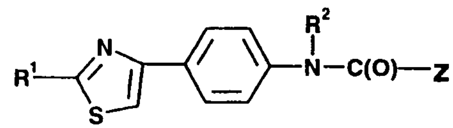
Entry No.	Z	HSV-1 IC_{50} μM	HSV-1 EC_{50} μM	ELISA CMV EC_{50} μM	PRA CMV EC_{50} μM	FAB/MS (*m/z*) $(MH)^+$
420		13			42	478
421					13	459
422		1.8			6.8	457
423	$CH_2CH_2CH_2CH_2C(O)N(CH_2Ph)_2$				12	499

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

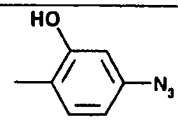
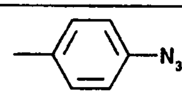
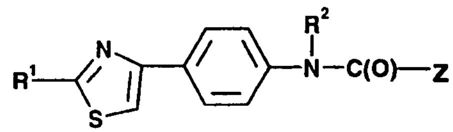
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
424	$CH_2CH_2CH_2CH_2CH_2NH_2$				30	305
425	$CH_2CH_2NH_2$				35	263
426		0.81				353
427		0.47				337

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

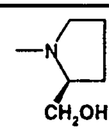
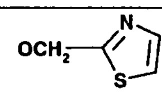
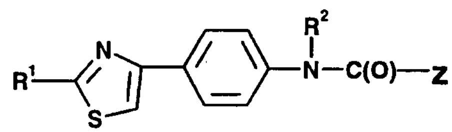
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
428		19			>27	819
429					30	333
430	(*S*)-$CH(NH_2)(CH_2)_4NHC(O)OCH_2Ph$				1.4	454
431	(*S*)-$CH(NHCH_2Ph)(CH_2)_4NHC(O)OCH_2Ph$				10	544
432	(*S*)-$CH_2C(O)NHCH(Me)Ph$	1.3			4.5	381
433	(*R*)-$CH(NH_2)(CH_2)_4NHC(O)OCH_2Ph$				17	454

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

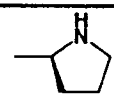
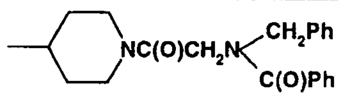
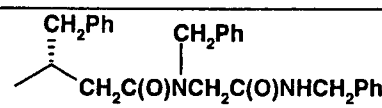
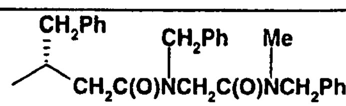
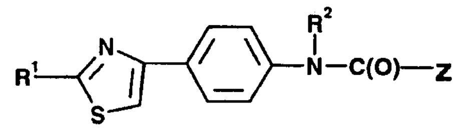
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
434		69	10		>55	289
435		20			7.2	554
436					7.8	618
437		2			17	632

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

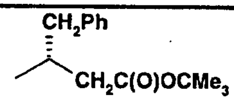
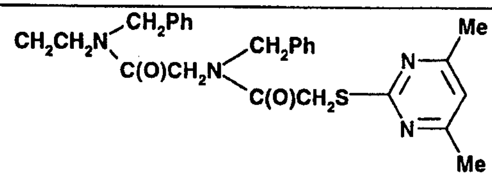
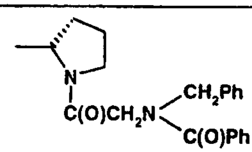
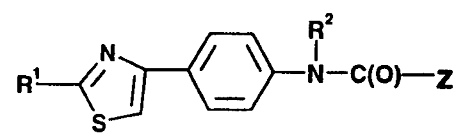
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
438		0.12			17	438
439					18	680
440		5.4	8.6		36	540

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

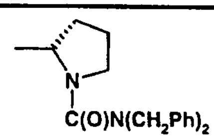
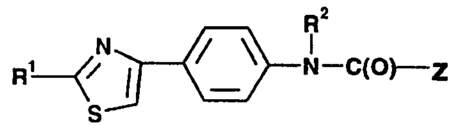
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
441		2.1	0.91		14	512
442	$CH_2CH_2N(CH_2Ph)C(O)CH_2N(CH_2Ph)C(O)OCMe_3$	0.69			7.6	600
443	$CH_2CH_2N(CH_2Ph)C(O)CH_2OCH_2Ph$				19	501

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

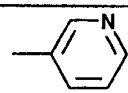
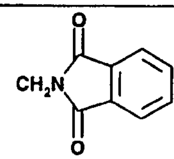
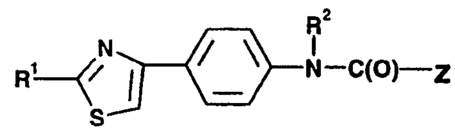
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
444	$CH_2CH_2N(CH_2Ph)C(O)CH_2CH_2NHC(O)OCMe_3$				23	524
445		22	7.5		>38	297
446		26	>27		>81	379
447	$CH_2CH_2NH_2$				35	263

TABLE 4

Compound of formula 1 having the structure

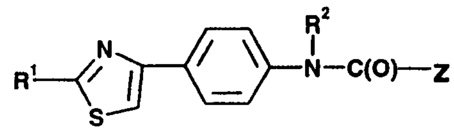


wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
448	$CH_2CH_2NHC(O)CH_2N(CH_2Ph)C(O)Ph$	12			31	514
449	$CH_2CH_2NHC(O)CH_2N(CH_2Ph)_2$				2.8	500
450	$N(OH)-CH_2Ph$				40	341
451	$CH_2CH_2NHC(O)N(CH_2Ph)_2$				12	486
452	$CH(CH_2Ph)CH_2C(O)N(Me)CH_2Ph$				18	485

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

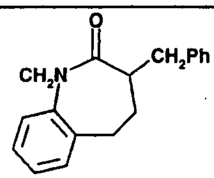
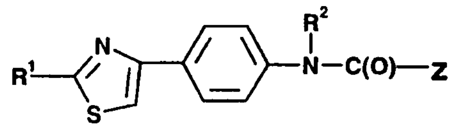
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
453	CH_2Ph $CH_2CHC(O)N(Me)CH_2Ph$				5.0	485
454		0.61	0.58			483

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

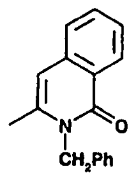
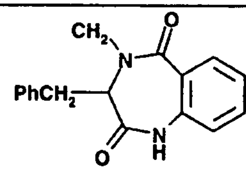
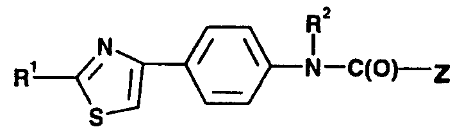
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
455		8.0	1.7			453
456		4.1	0.12			498

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

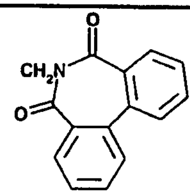
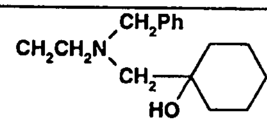
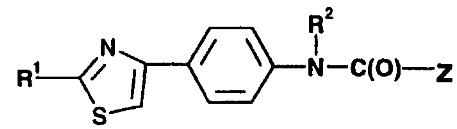
Entry No.	Z	HSV-1 IC_{50} μM	HSV-1 EC_{50} μM	ELISA CMV EC_{50} μM	PRA CMV EC_{50} μM	FAB/MS (*m/z*) $(MH)^+$
457		5.6	>14			455
458		1.3			>9.2	465

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

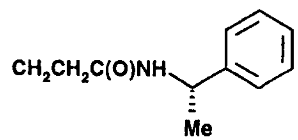
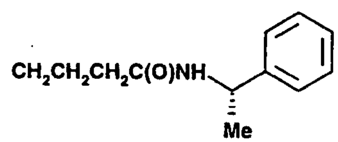
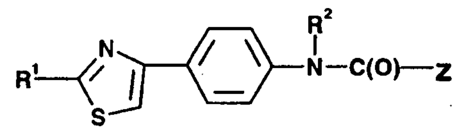
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
459		11.3			7.5	395
460		15			31	408
461	$CH_2CH_2CH_2C(O)N(CH_2Ph)_2$	3.8			13	485

TABLE 4

Compound of formula 1 having the structure



wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

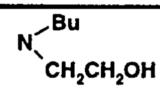
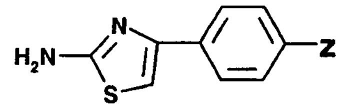
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
462		4.8			25	335
463	$CH_2CH_2C(O)N(CH_2Ph)_2$	2			20	471

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

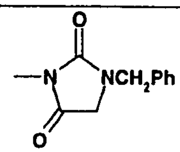
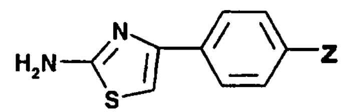
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
501	$NHCH_2C(O)N(Me)CH_2Ph$	>100	>37	33		353
502	$NHCH_2C(O)NHCH_2Ph$	>100	>44	63		339
503		21	8.2	56		365
504	$CH_2NHC(O)CH_2N(CH_2Ph)C(O)Ph$	26	3.9	19		457

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

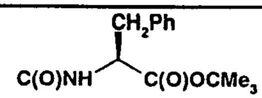
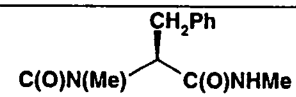
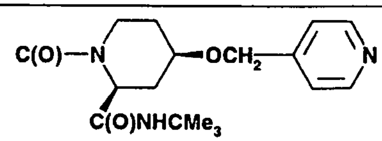
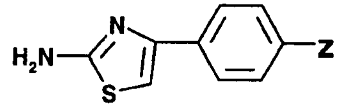
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
505		15	5.0	30	>21	424
506		>50	16	25	75	395
507		60			>86	494

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

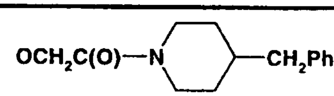
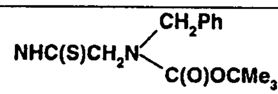
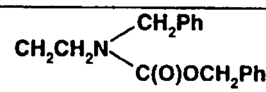
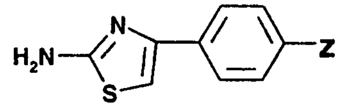
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
508		22			>19	408
509	$OCH_2C(O)N(Me)CMe_3$	45			>76	319
510	$OCH_2C(S)NHCH_2Ph$	5.5			>18	356
511		0.42			12	455
512		>50			9	444
513	$NHC(S)NHCH_2Ph$				33	341

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

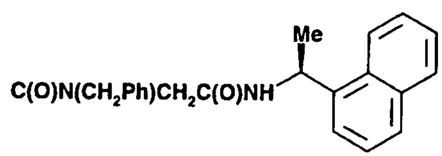
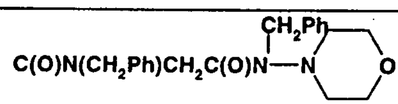
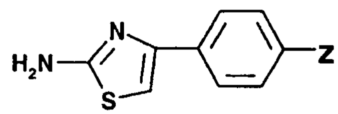
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
514					30	521
515					40	542
516	C(O)OMe				43	235
517	$CH_2CH_2NH\text{-}S(O)_2\text{-}CH_2Ph$				38	374

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

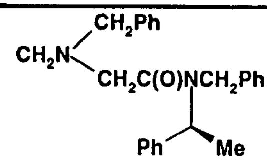
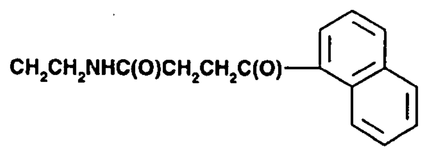
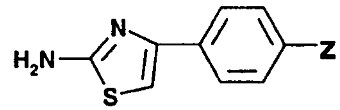
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
518					10	547
519	$CH_2CH_2NHC(O)CH_2CH_2C(O)Ph$	49			8.1	380
520					9.5	430

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

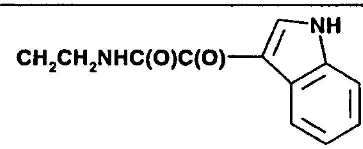
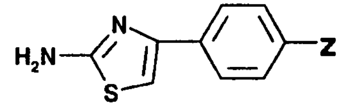
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
521	$CH_2CH_2NHC(O)CH_2N(CH_2Ph)C(O)Ph$	26			4.3	471
522	$CH_2CH_2NHC(O)CH_2N(CH_2Ph)C(O)OCMe_3$				7.3	467
523		>100			3	391

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

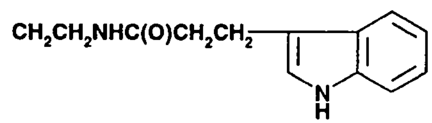
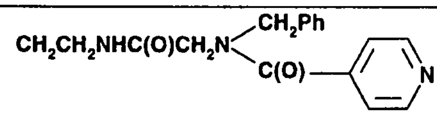
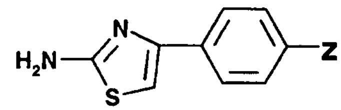
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
524					16	391
525	$CH_2CH_2N(CH_2Ph)C(O)CH_2Ph$				7	428
526	$CH_2CH_2N(CH_2Ph)S(O)_2CH_2Ph$				9.4	464
527					22	472

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

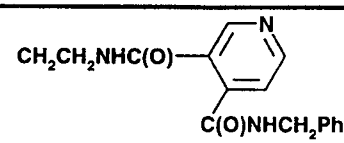
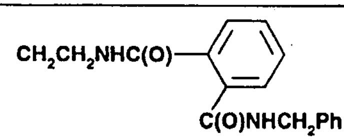
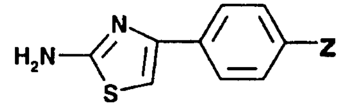
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
528					30	458
529	$CH_2CH_2NHC(O)CH_2CH_2C(O)NHCH_2Ph$				12	409
530		2.4			18	457

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

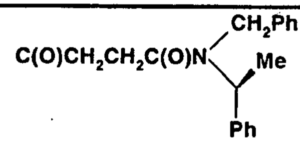
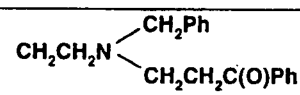
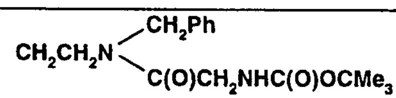
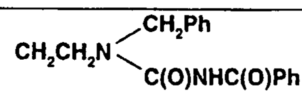
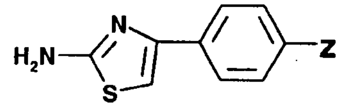
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
531		12			18	485
532		32			18	470
533					1.8	467
534		>100			4.2	470

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

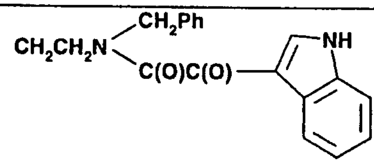
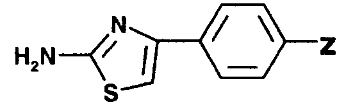
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
535	$CH_2CH_2NHC(O)CH_2NHC(O)OCMe_3$				38	377
536		0.15			15	481
537	$C(O)NHCH_2CH_2N(CH_2Ph)C(O)Ph$	0.60			19	457
538	$C(O)NHCH_2CH_2N(CH_2Ph)C(O)CH_2Ph$				16	471

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

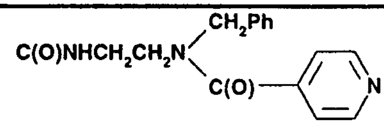
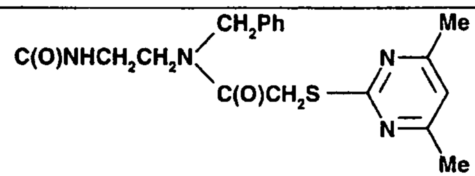
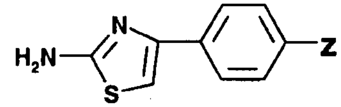
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
539					23	458
540					19	533
541	$C(O)NHCH_2CH_2N(CH_2Ph)C(O)OCMe_3$	10			22	453

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

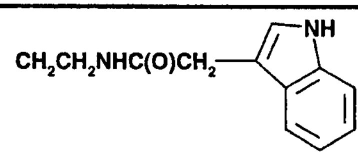
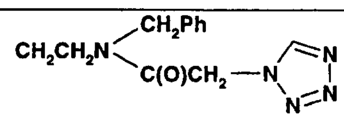
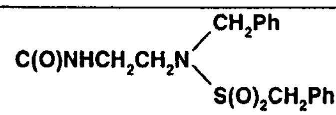
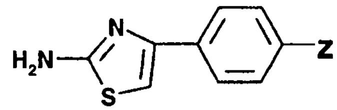
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
542					27	376
543					18	420
544					14	507

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

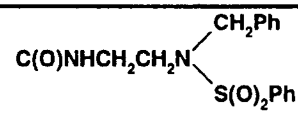
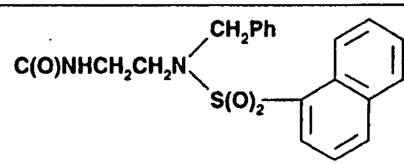
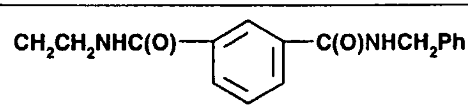
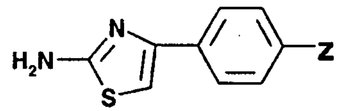
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
545					5.2	493
546					18	543
547		40			13	457

TABLE 5

Compound of formula 1 having the structure

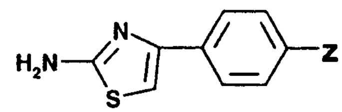


wherein Z is designated as follows:

Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
548	$CH_2CH_2N(CH_2Ph)C(O)C(O)Ph$	>100			2.2	442
549	$CH_2CH_2NHCH_2C(O)N(CH_2Ph)_2$				15	457
550	$CH_2CH_2NHC(O)CH(CH_2CH_2Ph)\text{-}NHC(O)OCMe_3$				22	481
551	$CH_2CH_2N(CH_2Ph)C(O)CH_2NHC(O)CH_2Ph$				13	484

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

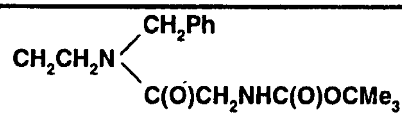
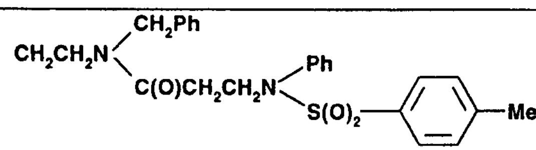
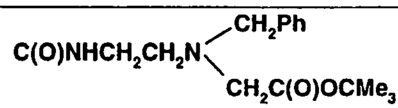
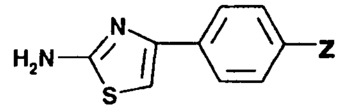
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
552					23	464
553					30	611
554		14			15	467

TABLE 5

Compound of formula 1 having the structure

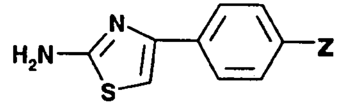


wherein Z is designated as follows:

Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
555	$CH_2CH_2N(CH_2Ph)C(O)CH_2NHC(O)NHPh$				15	486
556	$C(O)NHCH_2CH_2N(CH_2Ph)CH_2C(O)NHPh$				21	486
557	$C(O)NHCH_2CH_2N(CH_2Ph)CH_2C(O)NHCH_2Ph$				22	500

TABLE 5

Compound of formula 1 having the structure

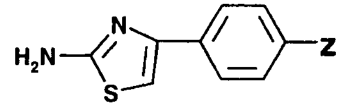


wherein Z is designated as follows:

Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
558	$CH_2CH_2N(CH_2Ph)C(O)CH_2NHC(O)NHCMe_3$				16	466
559	$CH_2CH_2N(CH_2Ph)C(O)CH_2NHC(O)CH_2N(CH_2Ph)C(O)OCMe_3$				13	614
560	$CH_2N(CH_2Ph)C(O)CH_2NHC(O)OCMe_3$				17	453

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

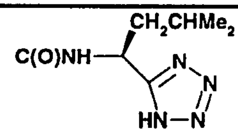
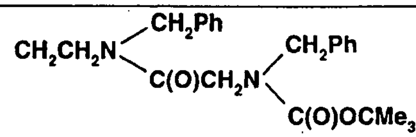
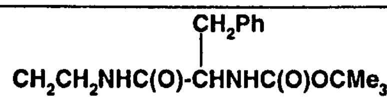
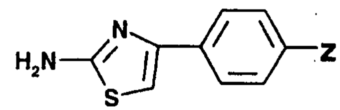
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
561					40	358
562					4.2	557
563					18	467
564	$CH_2NHCH_2C(O)N(CH_2Ph)_2$	10				443

TABLE 5

Compound of formula 1 having the structure



wherein Z is designated as follows:

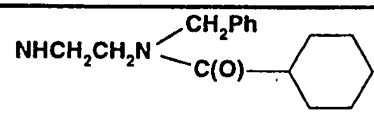
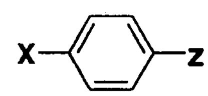
Entry No.	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
565		0.88	0.27	>4.0		435

TABLE 6

Compound of formula 1 having the structure



wherein X and Z are designated as follows:

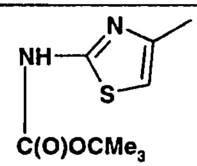
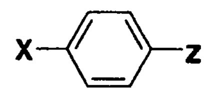
Entry No.	X	Z	HSV-1 IC_{50} μM	HSV-1 EC_{50} μM	ELISA CMV EC_{50} μM	PRA CMV EC_{50} μM	FAB/MS (*m/z*) $(MH)^+$
601	H	$NHC(O)CH_2N(CH_2Ph)C(O)Ph$	>50	>28	41		345
602	H	$NHC(O)CH_2N(CH_2Ph)C(O)OCMe_3$	>50	>34	36		341
603		NHC(O)NH-$CHPr_2$				1.6	432

TABLE 6

Compound of formula 1 having the structure



wherein X and Z are designated as follows:

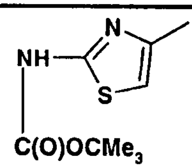
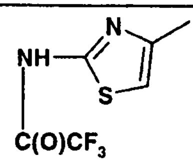
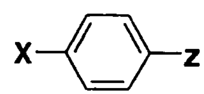
Entry No.	X	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
604		$NHC(S)NBu_2$				17	463
605		$NHC(O)NBu_2$				35	443

TABLE 6

Compound of formula 1 having the structure



wherein X and Z are designated as follows:

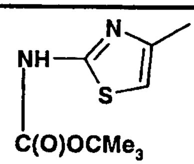
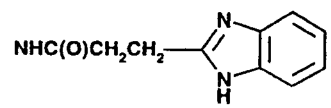
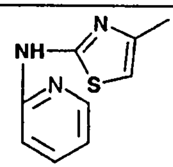
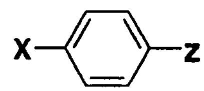
Entry No.	X	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
606						5.3	464
607		NHC(O)NBu2				2.2	424

TABLE 6

Compound of formula 1 having the structure



wherein X and Z are designated as follows:

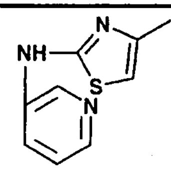
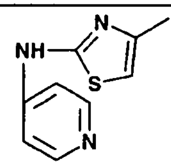
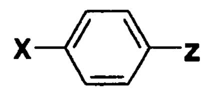
Entry No.	X	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
608		NHC(O)NBu$_2$				3.8	424
609		NHC(O)NBu$_2$				>11	424

TABLE 6

Compound of formula 1 having the structure



wherein X and Z are designated as follows:

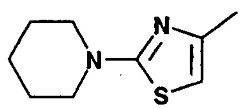
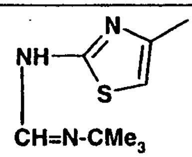
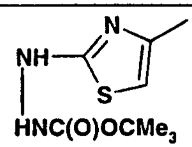
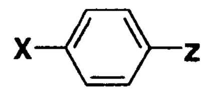
Entry No.	X	Z	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (*m/z*) $(MH)^+$
610		$NHC(O)NBu_2$				46	415
611		$NHC(O)CH_2CH_2N(CH_2Ph)_2$	>100			22	526
612		$NHC(O)NBu_2$				27	462

TABLE 6

Compound of formula 1 having the structure



wherein X and Z are designated as follows:

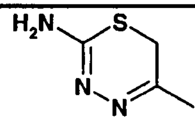
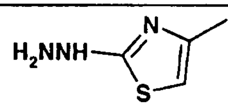
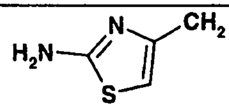
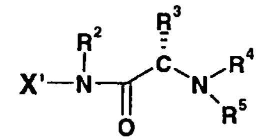
Entry No.	X	Z	HSV-1 IC_{50} μM	HSV-1 EC_{50} μM	ELISA CMV EC_{50} μM	PRA CMV EC_{50} μM	FAB/MS (*m/z*) $(MH)^+$
613		$NHC(O)NBu_2$	69			19	362
614		$NHC(O)NBu_2$	47			4.7	362
615		$NHC(O)CH_2CH_2N(CH_2Ph)_2$	>100			16	457

TABLE 7

Compound of formula 1' having the structure



wherein R^2 is H, R^3, R^4 and R^5 and X' are designated as follows:

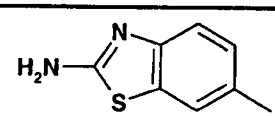
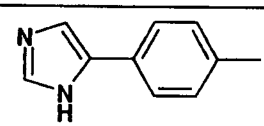
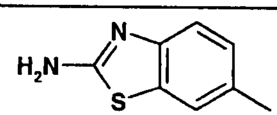
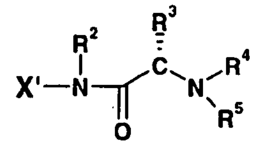
Entry No.	X'	R^3	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (MH^+)
701		H	CH_2Ph	C(O)OCMe$_3$	>50	>34	48		413
702		CH_2Ph	H	C(O)OCMe$_3$	>50	16	40		407
703		CH_2Ph	H	C(O)OCMe$_3$	>50		25		413

TABLE 7

Compound of formula 1' having the structure



wherein R^2 is H, R^3, R^4 and R^5 and X' are designated as follows:

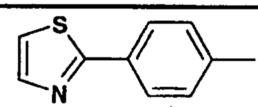
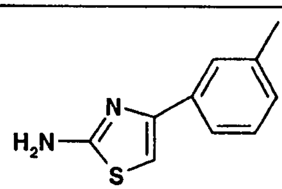
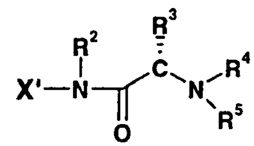
Entry No.	X'	R^3	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (MH^+)
704		CH_2Ph	H	$C(O)OCMe_3$	1.4			>8	424
705		H	H	CH_2Ph	>100	>42	18		339

TABLE 7

Compound of formula 1' having the structure



wherein R^2 is H, R^3, R^4 and R^5 and X' are designated as follows:

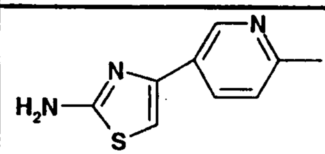
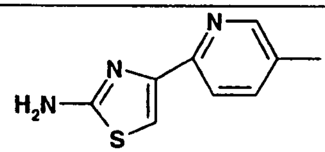
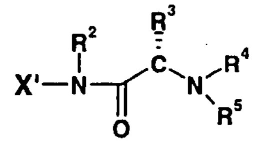
Entry No.	X'	R^3	R^4	R^5	HSV-1 IC_{50} μM	HSV-1 EC_{50} μM	ELISA CMV EC_{50} μM	PRA CMV EC_{50} μM	FAB/MS (MH^+)
706		H	CH_2Ph	$C(O)OCMe_3$	0.54			31	440
707		H	CH_2Ph	$C(O)OCMe_3$	2.7				440

TABLE 7

Compound of formula 1' having the structure



wherein R^2 is H, R^3, R^4 and R^5 and X' are designated as follows:

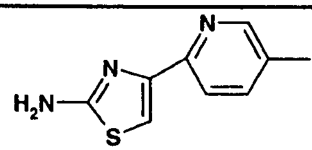
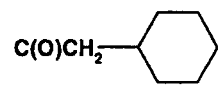
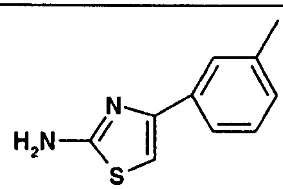
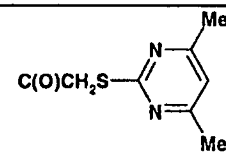
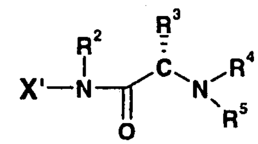
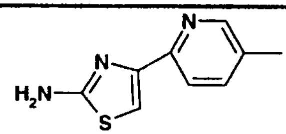
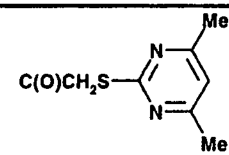
Entry No.	X'	R^3	R^4	R^5	HSV-1 IC_{50} µM	HSV-1 EC_{50} µM	ELISA CMV EC_{50} µM	PRA CMV EC_{50} µM	FAB/MS (MH^+)
708		H	CH_2Ph		6.6			7.6	464
709		H	CH_2Ph					19	519

TABLE 7

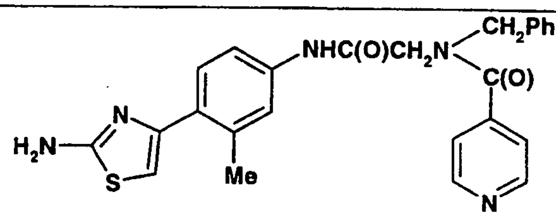
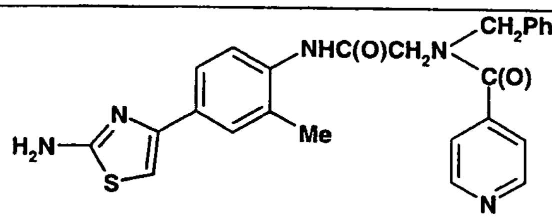
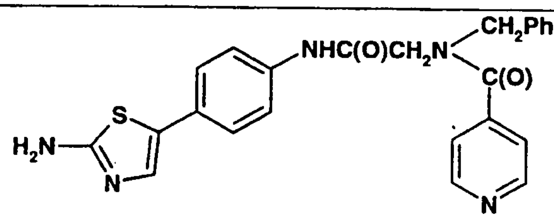
Compound of formula 1' having the structure



wherein R^2 is H, R^3, R^4 and R^5 and X' are designated as follows:

Entry No.	X'	R^3	R^4	R^5	HSV-1 IC_{50} μM	HSV-1 EC_{50} μM	ELISA CMV EC_{50} μM	PRA CMV EC_{50} μM	FAB/MS (MH^+)
710		H	CH_2Ph		>100			16	520

Additional compounds are the following:

Compound	HSV-1 IC_{50} µM
	25
	10% inhibition at 100 µM
	>100

In an embodiment of this invention, a preferred group of compound of preceding TABLES 1 to 6 are those designated as entry numbers 107, 109, 111 and 114 in TABLE 1; as entry numbers 201, 203, 205, 206 and 207 in TABLE 2; as entry numbers 305, 308, 313 and 314 in TABLE 3; as entry numbers 407, 412, 413, 427 and 438 in TABLE 4; and as entry numbers 511 and 536 in TABLE 5.

Claims:

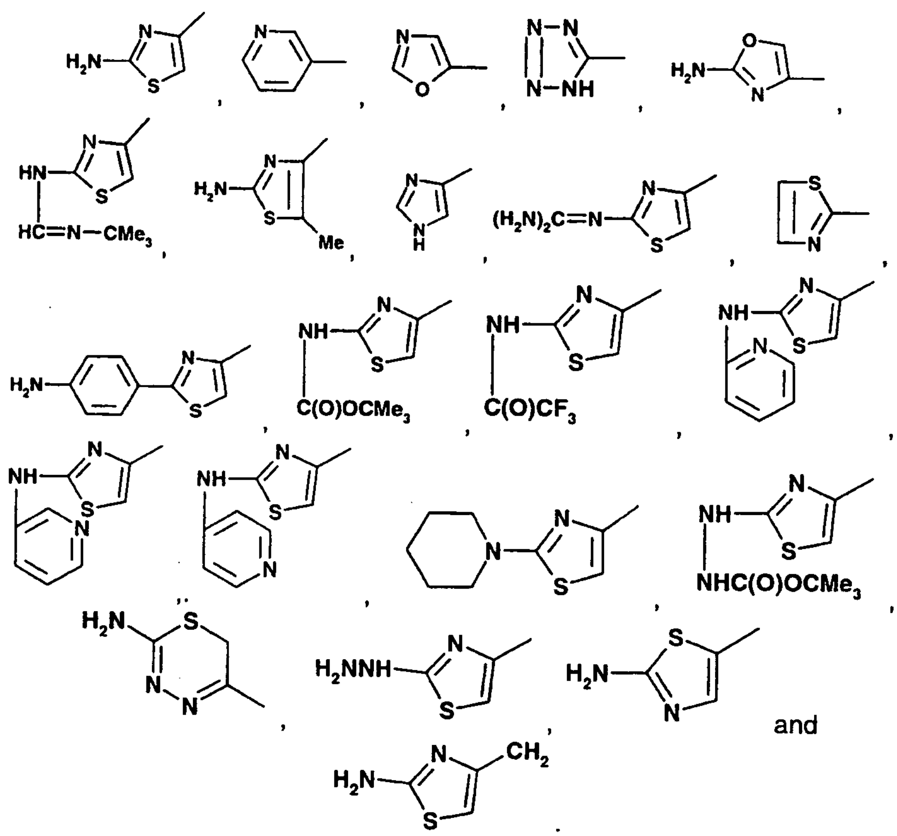
1. A compound of formula 1

$$\textbf{X-Aryl-Y-Z} \quad (1)$$

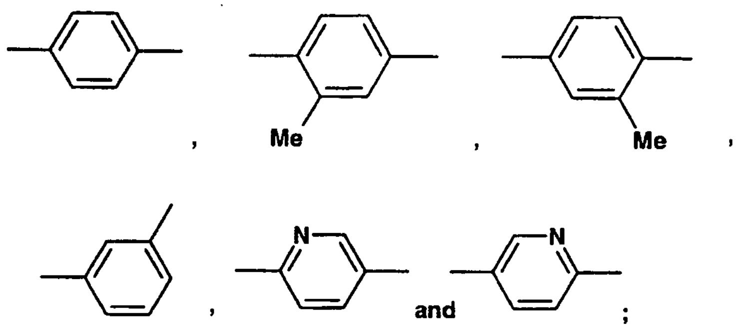
wherein

(i) **X** is selected from the group consisting of:

H, $H_2NC(O)NHCHMe$, $NH_2S(O)_2$—,



Aryl is selected from the group consisting of:



;

Y is $-N(R^2)-C(O)-CH(R^3)-$ wherein

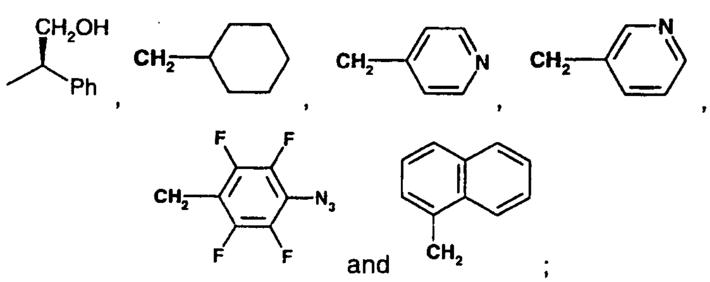
R^2 is H or lower alkyl, and

R^3 is H; lower alkyl; (lower cycloalkyl)-(lower alkyl) (e.g. CH_2-(cyclohexyl); phenyl(lower alkyl); phenyl(lower alkyl) monosubstituted, disubstituted or trisubstituted on the aromatic portion thereof with a substituent or substituents selected independently from the group consisting of halo, hydroxy, lower alkoxy, lower alkoxy, lower alkyl, azido and trifluoromethyl; CH_2-Het; or CH_2-(bicyclic heterocyclic system); and

Z is NR^4R^5 wherein

R^4 is H, phenyl(lower alkyl) (e.g. CH_2Ph) or phenyl(lower alkyl) monosubstituted, disubstituted or trisubstituted on the aromatic portion thereof with a substituent or substituents selected independently from the group consisting of halo, hydroxy, lower alkoxy, lower alkyl, azido and trifluoromethyl, or

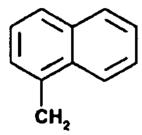
R^4 is selected from the group consisting of:

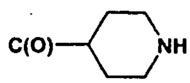


;

and **R**^{5} is selected from the group consisting of:

C(O)$(CH_2)_5NH_2$; $CH_2C(O)N(Me)CH_2Ph$; $CH_2C(O)NHCH_2Ph$; $C(O)CH_2OH$;



;


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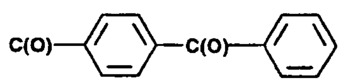
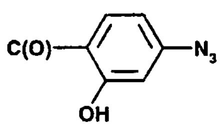


;



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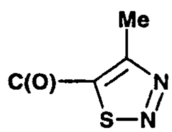
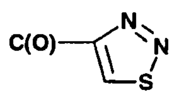
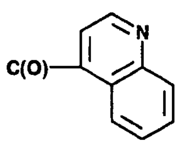
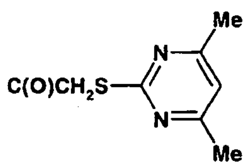
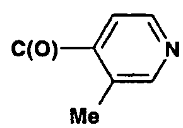


;


;

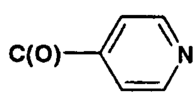


;


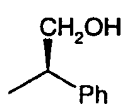
and


;

or **R**^{5} is

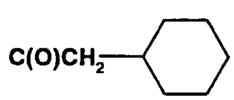


,

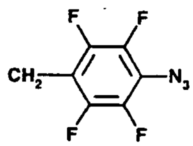
when **R**^{4} is 

or a mono-, di- or trisubstituted phenyl(lower alkyl) wherein each substituent is on the aromatic portion and is selected independently from azido and trifluoromethyl;

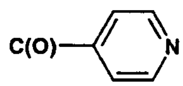
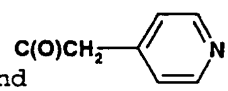
or **R**^{5} is



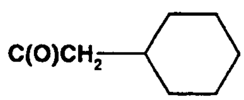
,

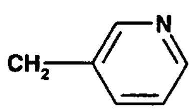
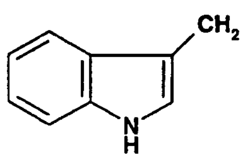
when $\mathbf{R^4}$ is  or a mono-, di- or trisubstituted phenyl(lower alkyl) wherein each substituent is on the aromatic portion and is selected independently from azido and trifluoromethyl;

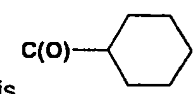
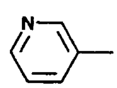
or $\mathbf{R^5}$ is selected from the group consisting of:

C(O)Ph,  and ,

when $\mathbf{R^3}$ is CH_2-(cyclohexyl);

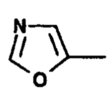
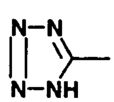
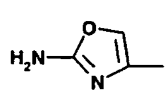
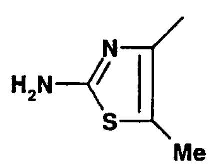
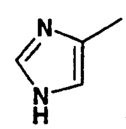
or $\mathbf{R^5}$ is  or $C(O)OCMe_3$ when $\mathbf{R^3}$ is $CH_2CH_2CH_2NH_2$,

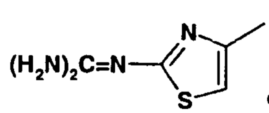
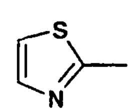
 or ;

or $\mathbf{R^5}$ is , when **X** is ;

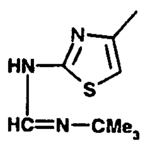
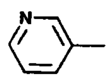
or $\mathbf{R^5}$ is C(O)Ph,

when **X** is $NH_2S(O)_2$, $H_2NC(O)NHCHMe$,

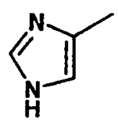
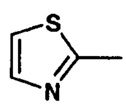
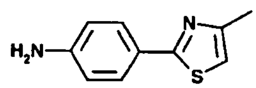
, , , , ,

 or ;

or R^5 is phenyl(lower alkyl) or mono-, di- or trisubstituted phenyl(lower alkyl) wherein each substituent is on the aromatic portion and is selected independently from azido and trifluoromethyl,

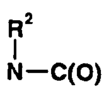
when **X** is  or  ;

or R^5 is $C(O)OCMe_3$,

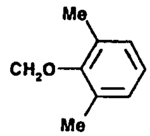
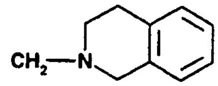
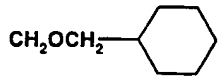
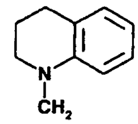
when **X** is  ,  or  ;

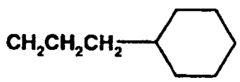
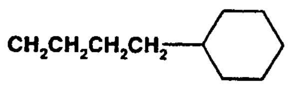
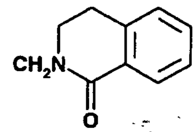
or

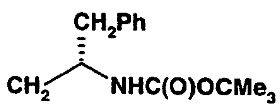
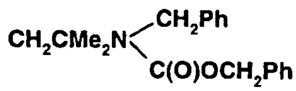
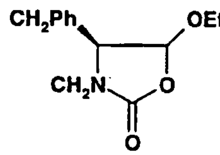
(ii) **X** and **Aryl** are as defined above;

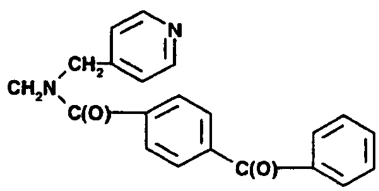
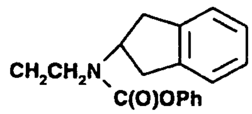
Y is  wherein R^2 is H or lower alkyl, and

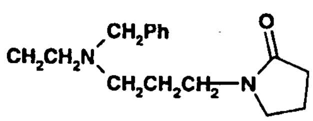
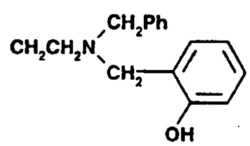
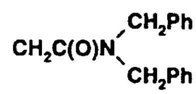
Z is selected from the group consisting of:
CH_2OCH_2Ph, CH_2OPh, OCH_2CHMe_2, CH_2CH_2Ph, $CH_2CH_2CH_2Ph$, CH_2SCH_2Ph, CH=CHPh, $CH_2CH_2CH_2CH_2C(O)NPh_2$, $CH_2CH_2CH_2CH_2CH_2NH_2$, $CH_2CH_2NH_2$, $CH(NH_2)(CH_2)_4NHC(O)OCH_2Ph$, (*S*)-$CH(NHCH_2Ph)(CH_2)_4NHC(O)OCH_2Ph$, (*S*)-$CH_2C(O)NHCH(Me)Ph$, (*R*)-$CH(NH_2)(CH_2)_4NHC(O)OCH_2Ph$, $CH_2CH_2NH_2$, $CH_2CH_2NHC(O)CH_2N(CH_2Ph)_2$, $CH_2CH_2NHC(O)N(CH_2Ph)_2$, $CH_2CH_2CH_2C(O)N(CH_2Ph)_2$, $CH_2CH_2C(O)N(CH_2Ph)_2$,

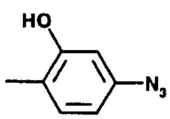
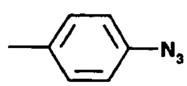
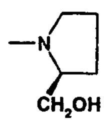
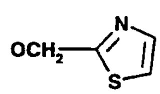
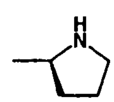
 ,  ,  ,  ,

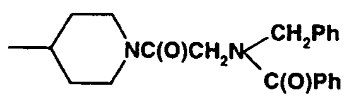
 ,  ,  ,

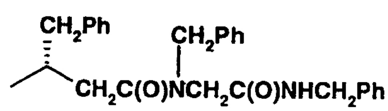
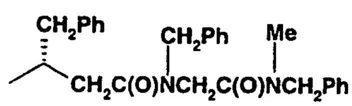
 ,  ,  ,

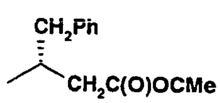
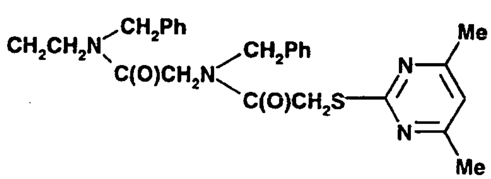
 ,  ,

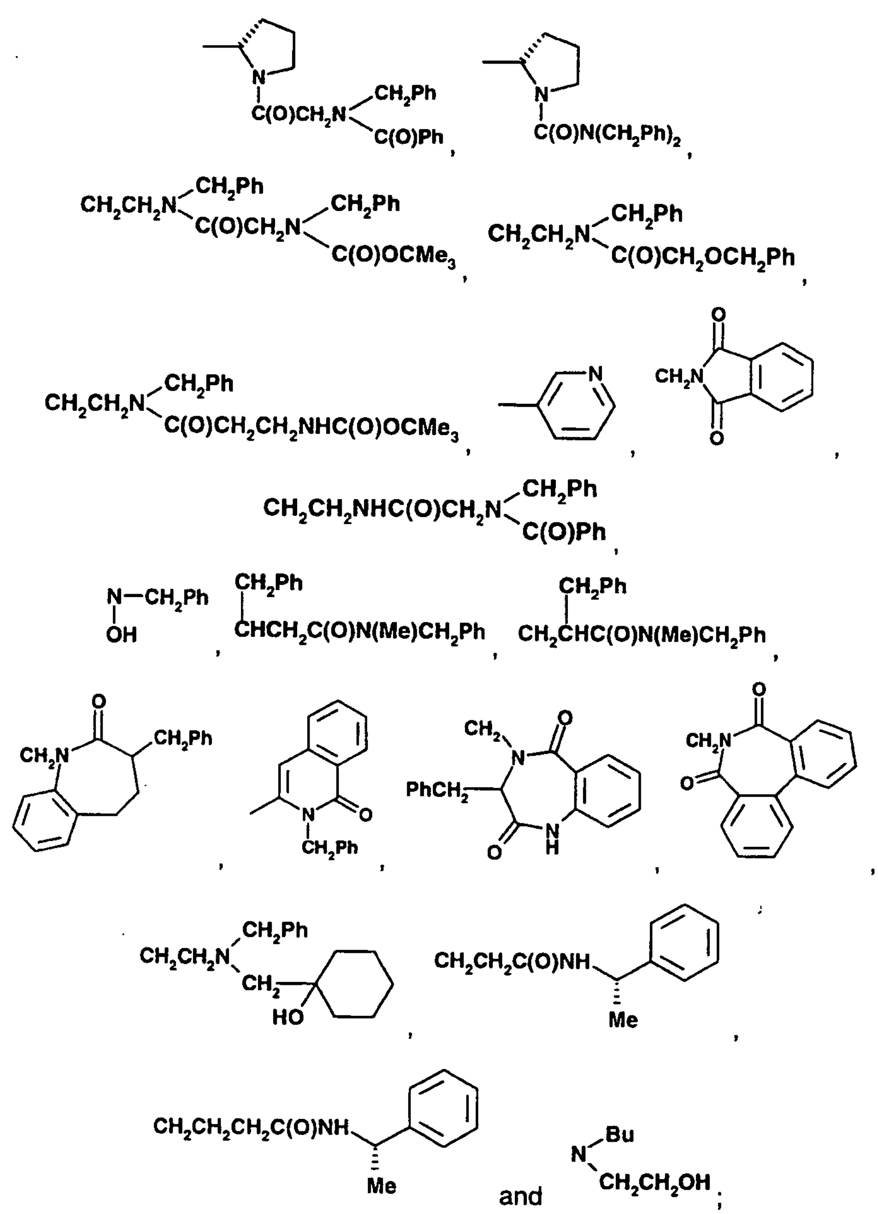
 ,  ,  ,

 ,  ,  ,  ,  ,

 ,

(*S*)-  ,  ,

 ,  ,



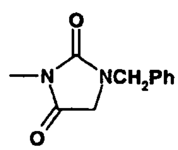
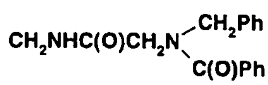
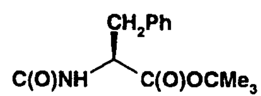
or

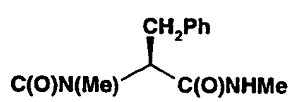
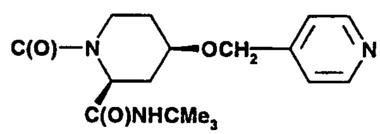
(iii) X and **Aryl** are as defined above;

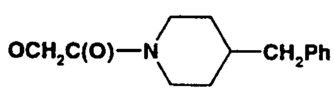
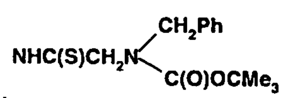
Y is absent (i.e. a valence bond); and

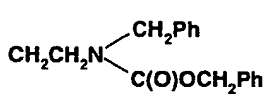
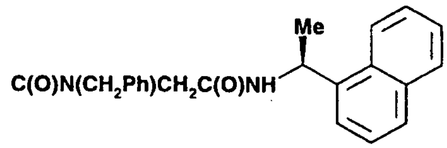
Z is selected from the group consisting of:

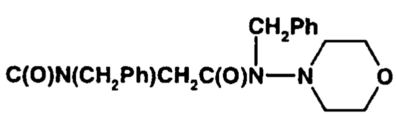
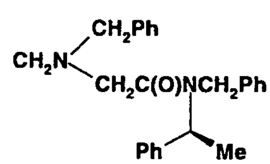
$NHCH_2C(O)N(Me)CH_2Ph$, $NHCH_2C(O)NHCH_2Ph$, $OCH_2C(O)N(Me)CMe_3$, $OCH_2C(S)NHCH_2Ph$, $NHC(S)NHCH_2Ph$, $C(O)OMe$, $CH_2CH_2NH\text{-}S(O)_2\text{-}CH_2Ph$, $CH_2CH_2NHC(O)CH_2CH_2C(O)Ph$, $CH_2CH_2N(CH_2Ph)C(O)CH_2Ph$, $CH_2CH_2N(CH_2Ph)S(O)_2CH_2Ph$, $CH_2CH_2NHC(O)CH_2CH_2C(O)NHCH_2Ph$, $CH_2CH_2NHC(O)CH_2NHC(O)OCMe_3$, $CH_2CH_2NHCH_2C(O)N(CH_2Ph)_2$, $CH_2NHCH_2C(O)N(CH_2Ph)_2$,

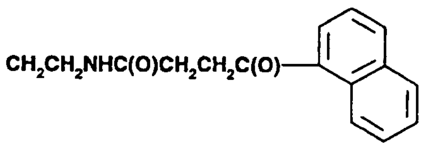
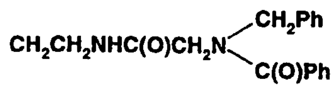
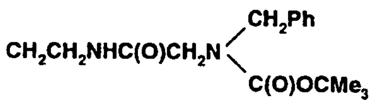
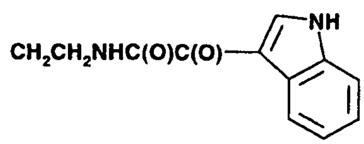
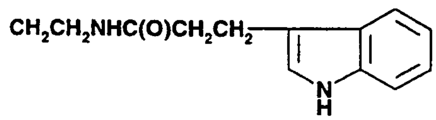
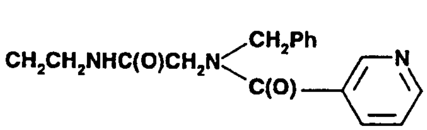
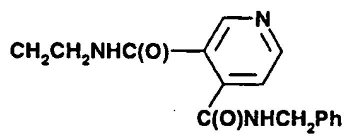
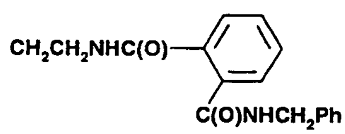
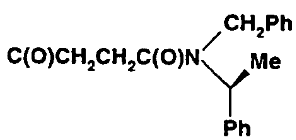
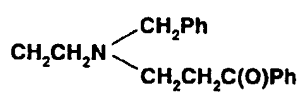
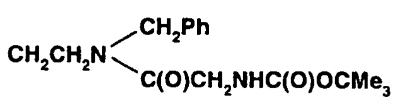
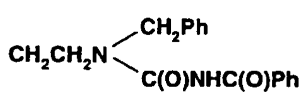
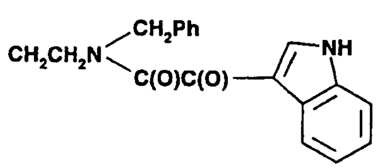
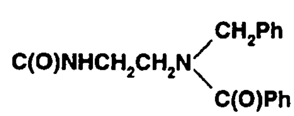
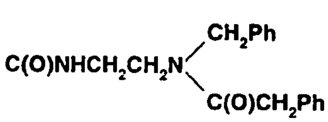
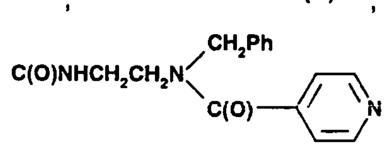
, , ,

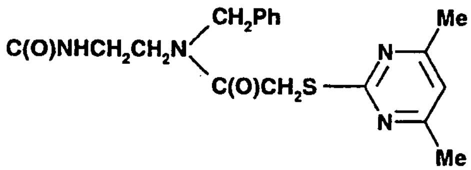
, ,

, ,

, ,

, ,

,
,
,
,
,
,
,
,
,
,
,
,
,
,
,
,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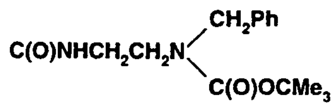
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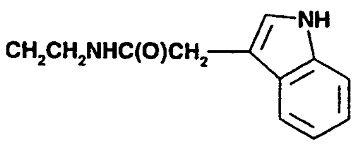
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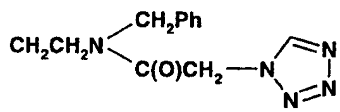
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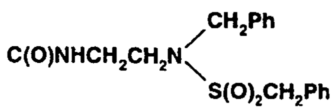
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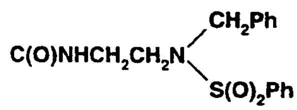
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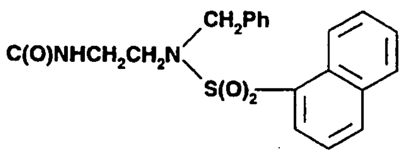
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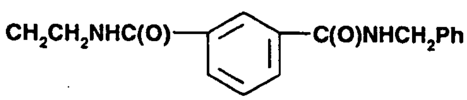
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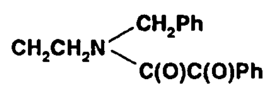
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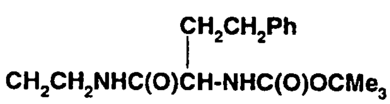
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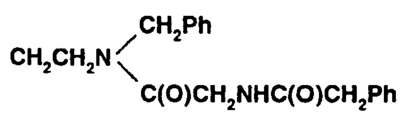
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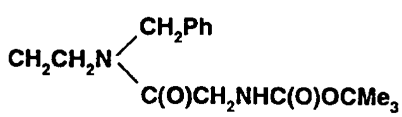
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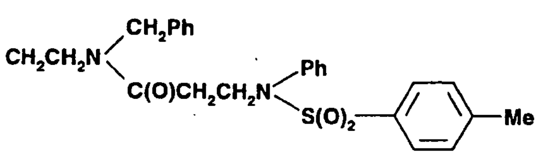
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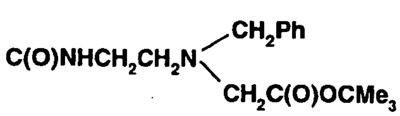
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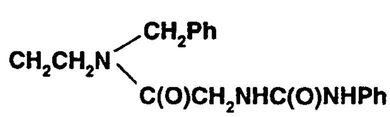
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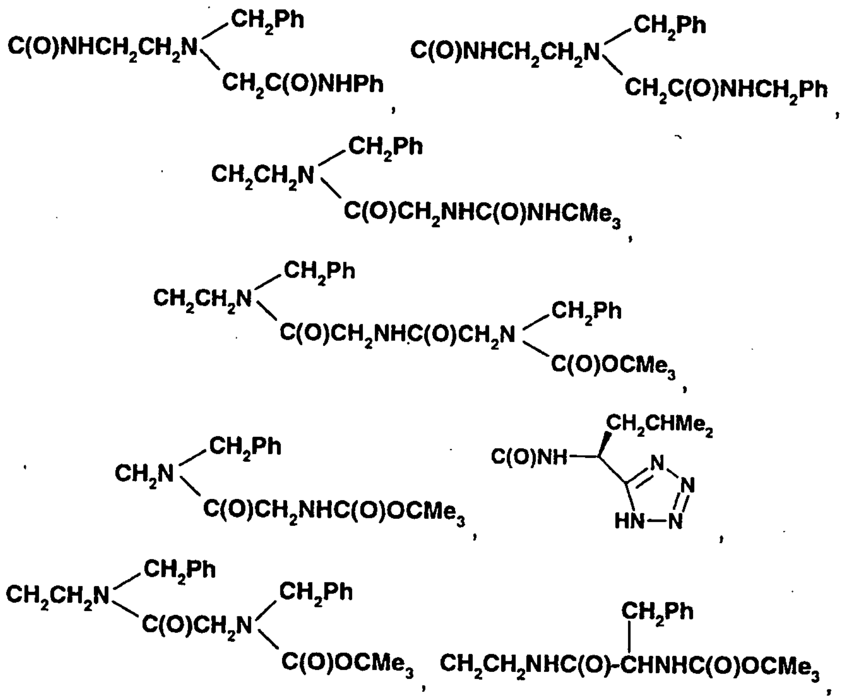
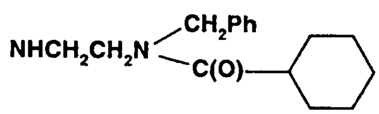
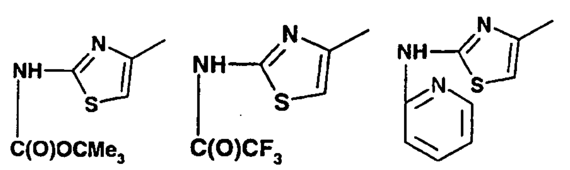
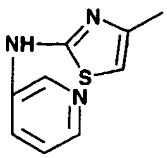
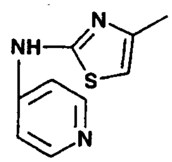
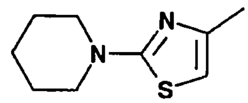
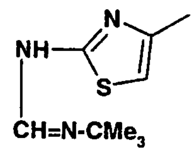


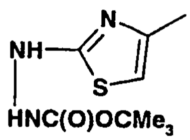
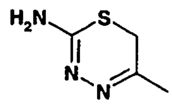
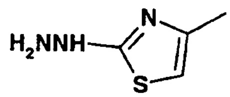
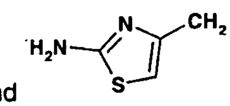
and  ;

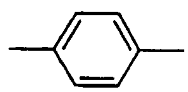
or

(iv) **X** is selected from the group consisting of:

H, 

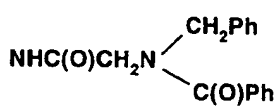
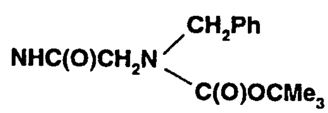
, , , ,

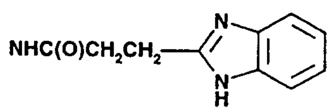
 ,  and ;

Aryl is ;

Y is absent; and

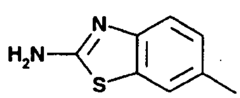
Z is selected from the group consisting of: NHC(O)NH-$CHPr_2$, NHC(S)NBu_2, NHC(O)NBu_2, NHC(O)$CH_2CH_2N(CH_2Ph)_2$,

, , and

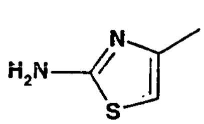
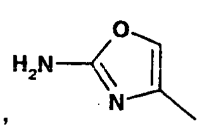
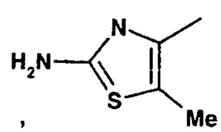
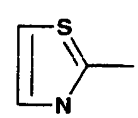
;

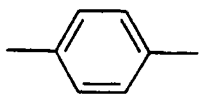
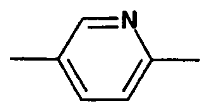
or

(v) **X** and **Aryl** together form **X'** which is defined as

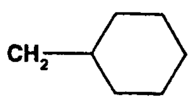
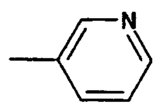
, and **Y** and **Z** are as defined in paragraph (i).

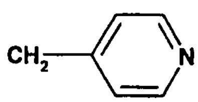
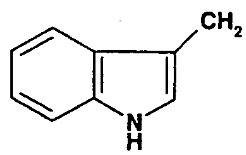
2. A compound according to claim 1, subsection (i), wherein **X** is

, ,  or ,

Aryl is  or ,

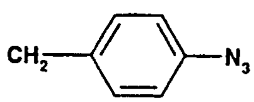
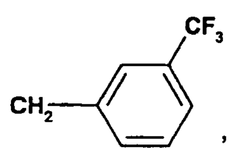
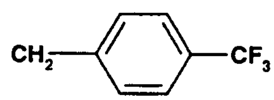
Y is $N(R^2)$—C(O)—$CH(R^3)$ wherein $\mathbf{R^2}$ is hydrogen and $\mathbf{R^3}$ is H,

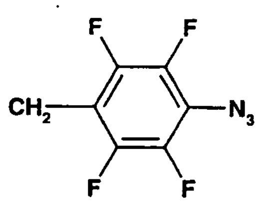
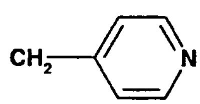
, CH_2Ph, ,

 or , and

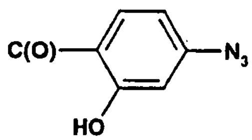
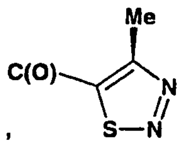
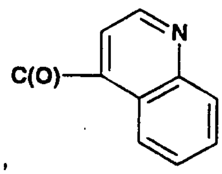
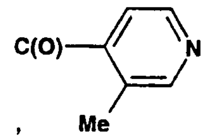
Z is NR^4R^5 wherein

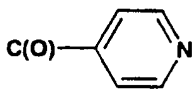
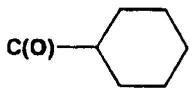
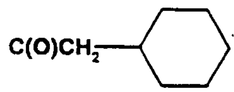
$\mathbf{R^4}$ is H, CH_2Ph,

, , 

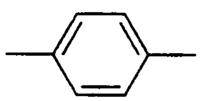
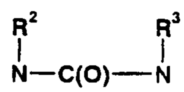
 or , and

$\mathbf{R^5}$ is

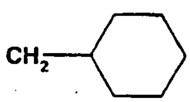
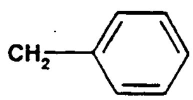
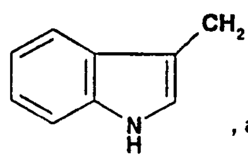
, , , ,

, , , C(O)Ph or C(O)CMe$_3$.

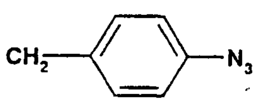
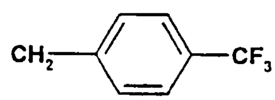
3. A compound according to claim 2 wherein X is defined in Claim 2,

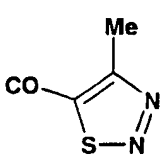
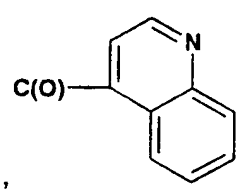
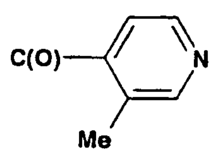
Aryl is , **Y is** 

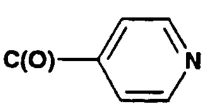
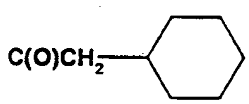
wherein **R**^{2} is H and **R**^{3} is H,

,  or , and

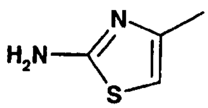
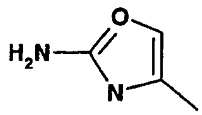
Z is NR^{4}R^5 wherein

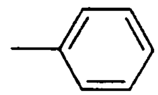
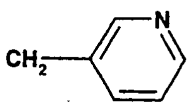
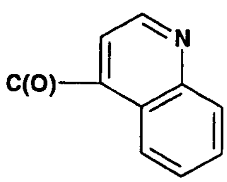
R^4 is H, CH$_2$Ph,  or , and

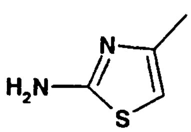
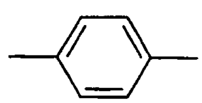
R^5 is , , ,

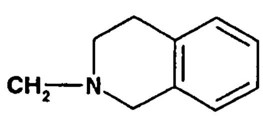
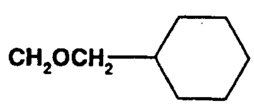
, , C(O)Ph or C(O)OCMe$_3$.

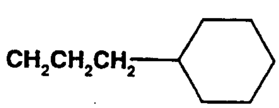
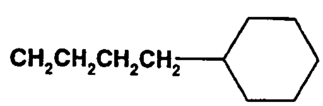
4. A compound according to claim 2 wherein **X** is

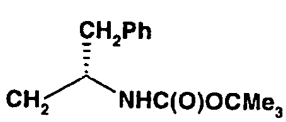
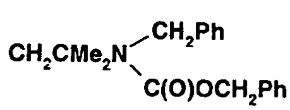
 or  .

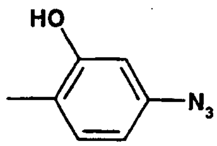
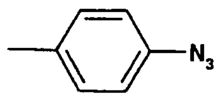
5. A compound according to claim 4 wherein **Aryl** is , **Y** is $N(R^2)-C(O)-CH(R^3)$ wherein $\mathbf{R^2}$ is H and $\mathbf{R^3}$ is H or ,and **Z** is NR^4R^5 wherein $\mathbf{R^4}$ is H or CH_2Ph, and $\mathbf{R^5}$ is , C(O)Ph or $C(O)OCMe_3$.

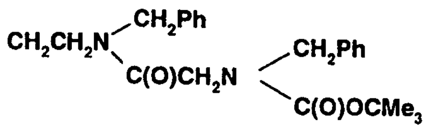
6. A compound according to claim 1 subsection (ii) wherein X is , Aryl is , Y is NH-C(O) and Z is

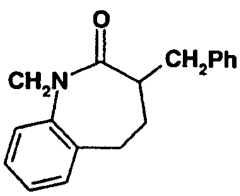
, ,

, ,

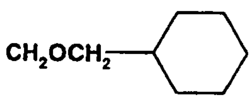
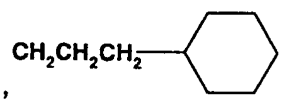
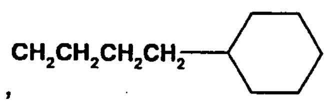
, ,

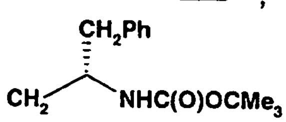
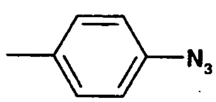
, ,

 or

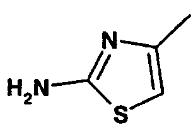
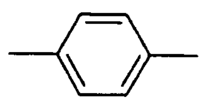


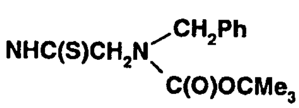
7. A compound according to claim 6 wherein Z is

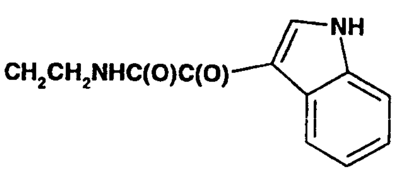
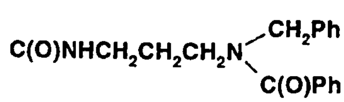
, , ,

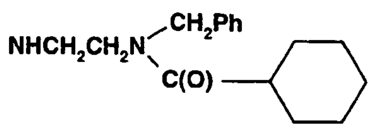
 or .

8. A compound according to claim 1, subsection (iii) wherein X is

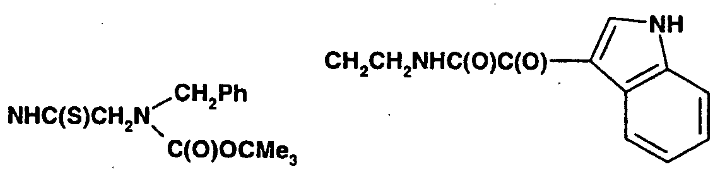
, Aryl is  and Z is

,

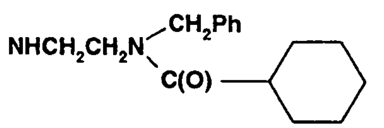
,  and



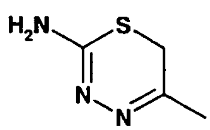
9. A compound according to claim 8 wherein Z is



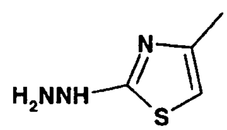
and



10. A compound according to claim 1, subsection (iv) wherein X is

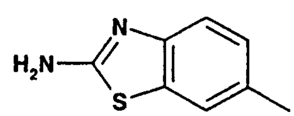


or

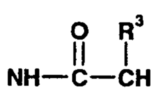


and Z is $NHC(O)NBu_2$.

11. A compound according to claim 1, subsection (v), wherein X and Aryl together form X^1 which is defined as

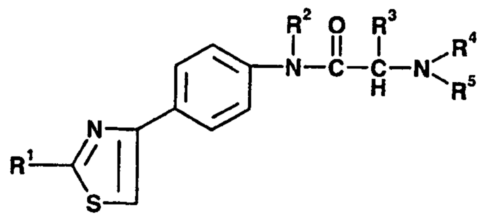


, Y is

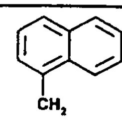
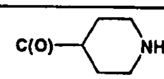
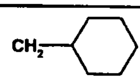
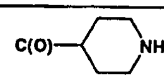
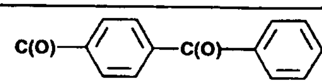
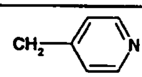
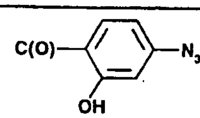
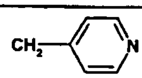
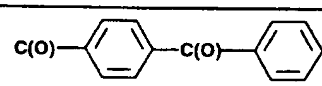
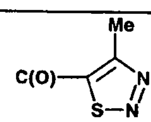
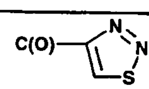


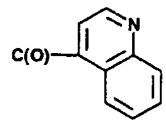
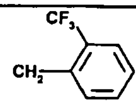
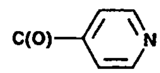
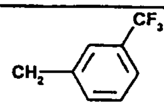
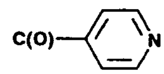
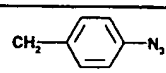
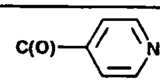
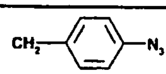
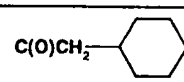
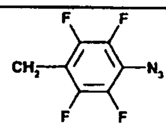
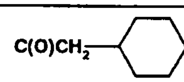
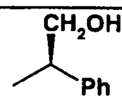
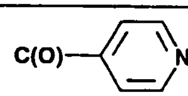
wherein R^3 is H or $PhCH_2$ and Z is NR^4R^5 wherein R^4 is H or CH_2Ph and R^5 is $C(O)OCMe_3$.

12. A compound according to claim 1, subsection (i), having the structure



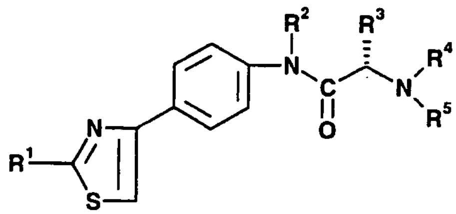
wherein R^1 is NH_2, R^2 is H, R^3 is H, and R^4 and R^5 are designated as follows:

Table 1 Entry No.	**R^4**	**R^5**
101	H	 ,
102	CH_2Ph	 ,
103		 ,
104	CH_2Ph	 ,
105		 ,
106		 ,
107	CH_2Ph	 ,
108	CH_2Ph	 ,

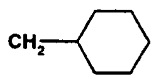
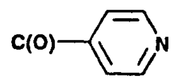
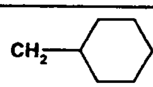
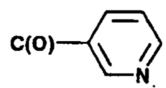
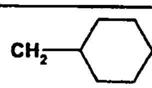
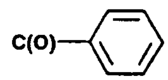
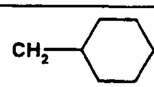
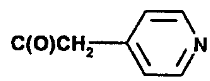
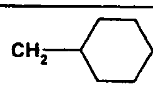
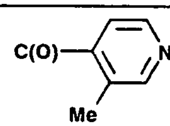
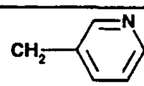
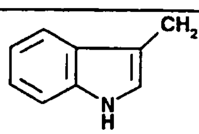
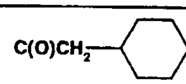
109	CH_2Ph		,
110			,
111			,
112	CH_2Ph	$C(O)(CH_2)_5NH_2$	,
113			,
114			,
115			,
116	CH_2Ph	$CH_2C(O)N(Me)CH_2Ph$	,
117	CH_2Ph	$CH_2C(O)NHCH_2Ph$	,
118	CH_2Ph	$C(O)CH_2OH$	, or
119			.

13. A compound according to claim 12 selected from the group consisting of compounds of entry numbers 107, 109, 111 and 114.

14. A compound according to claim 1, subsection (i), having the stucture

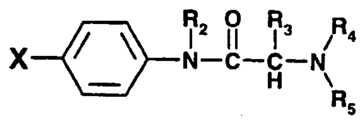


wherein R^1 is NH_2, R^2 is H, and R^3, R^4 and R^5 are designated as follows:

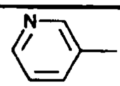
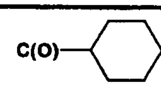
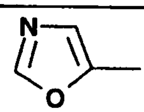
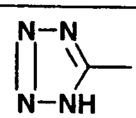
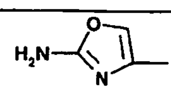
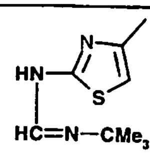
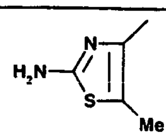
Table 2 Entry No.	R^3	R^4	R^5	
201		H		,
202		H		,
203		H		,
204		H		,
205		H		,
206		H	$C(O)OCMe_3$	,
207		H	$C(O)OCMe_3$	,
208	Entry 208 is the enantiomer at R^3 of Entry 207			, or
209	$(CH_2)_4NH_2$	CH_2P h		.

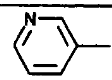
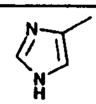
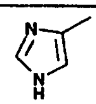
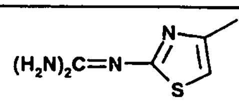
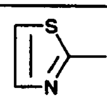
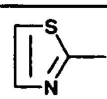
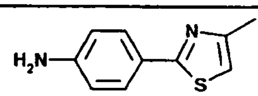
15. A compound according to claim 14 selected from the group consisting of compounds of entry numbers 201, 203, 205, 206 and 207.

16. A compound according to claim 1, subsection (i), having the structure



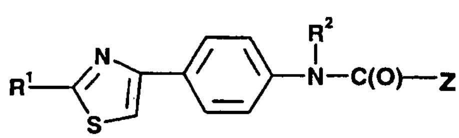
wherein R^2 and R^3 each is hydrogen and X, R^4 and R^5 are designated as follows:

Table 3 Entry No.	X	R^4	R^5
301		CH_2Ph	
302		CH_2Ph	C(O)Ph
303	$NH_2S(O)_2$—	CH_2Ph	C(O)Ph
304		CH_2Ph	C(O)Ph
305		CH_2Ph	C(O)Ph
306	$H_2NC(O)NHCHMe$-	CH_2Ph	C(O)Ph
307		H	$PhCH_2$
308		CH_2Ph	C(O)Ph

309		H	CH_2Ph	,
310		CH_2Ph	$C(O)OCMe_3$	,
311		CH_2Ph	$C(O)Ph$	,
312		CH_2Ph	$C(O)Ph$	,
313		CH_2Ph	$C(O)Ph$	,
314		CH_2Ph	$C(O)OCMe_3$	, or
315		CH_2Ph	$C(O)OCMe_3$	,

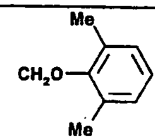
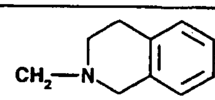
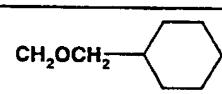
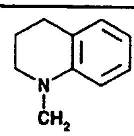
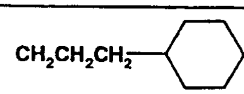
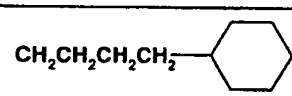
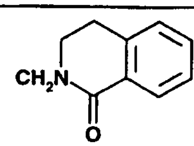
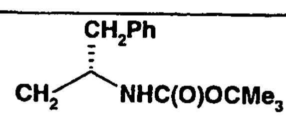
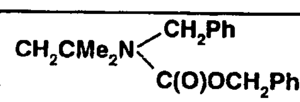
17. A compound according to claim 16 selected from the group consisting of compounds of entry numbers 305, 308, 313 and 314.

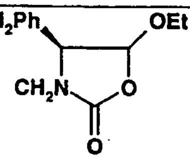
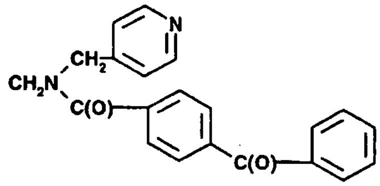
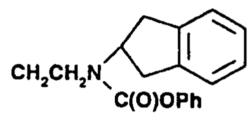
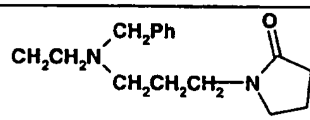
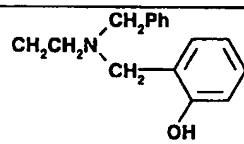
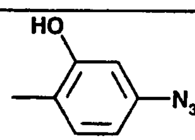
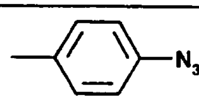
18. A compound according to claim 1, subsection (ii), having the structure

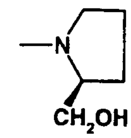
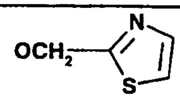
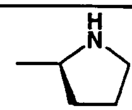
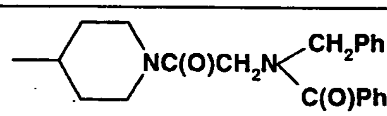
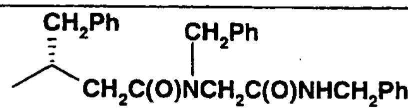
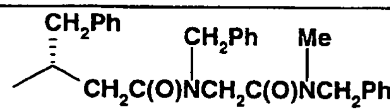
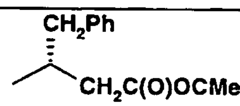
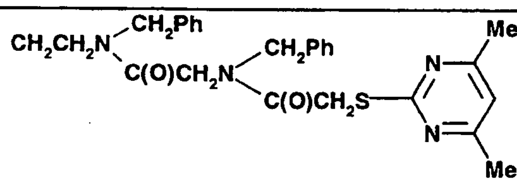


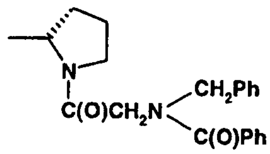
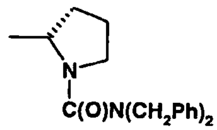
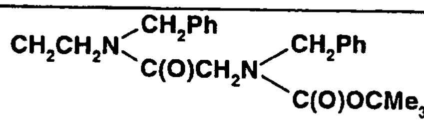
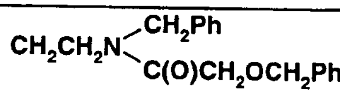
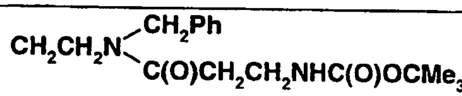
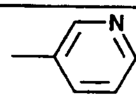
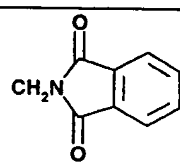
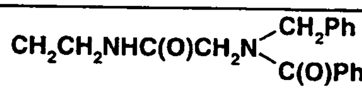
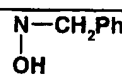
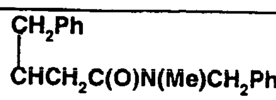
wherein R^1 is NH_2, R^2 is H and Z is designated as follows:

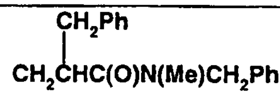
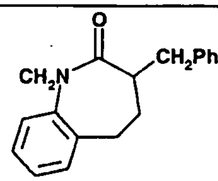
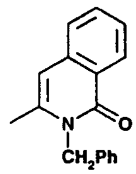
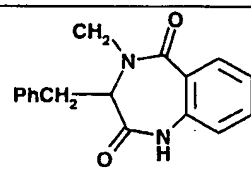
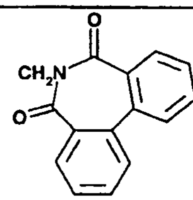
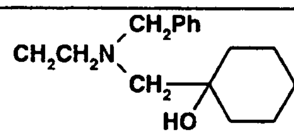
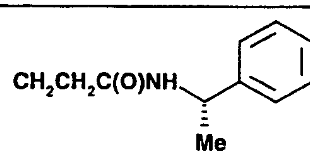
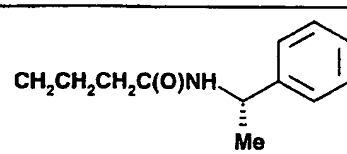
Table 4 Entry No.	Z	
401	CH_2OCH_2Ph	,

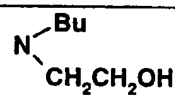
402	CH_2Oph	,
403		,
404		,
405	OCH_2CHMe_2	,
406	CH_2CH_2Ph	,
407		,
408		,
409	$CH_2CH_2CH_2Ph$	,
410	CH_2SCH_2Ph	,
411	CH=CHPh	,
412		,
413		,
414		,
415		,
416		,

417		,
418		,
419		,
420		,
421		,
422		,
423	$CH_2CH_2CH_2CH_2C(O)N(CH_2Ph)_2$	,
424	$CH_2CH_2CH_2CH_2CH_2NH_2$	,
425	$CH_2CH_2NH_2$	,
426		,
427		,

428	 ,
429	 ,
430	(S)-$CH(NH_2)(CH_2)_4NHC(O)OCH_2Ph$,
431	(S)-$CH(NHCH_2Ph)(CH_2)_4NHC(O)OCH_2Ph$,
432	(S)-$CH_2C(O)NHCH(Me)Ph$,
433	(R)-$CH(NH_2)(CH_2)_4NHC(O)OCH_2Ph$,
434	 ,
435	 ,
436	 ,
437	 ,
438	 ,
439	 ,

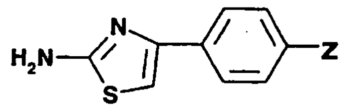
440		,
441		,
442		,
443		,
444		,
445		,
446		,
447	$CH_2CH_2NH_2$	,
448		,
449	$CH_2CH_2NHC(O)CH_2N(CH_2Ph)_2$	,
450		,
451	$CH_2CH_2NHC(O)N(CH_2Ph)_2$	,
452		,

453		,
454		,
455		,
456		,
457		,
458		,
459		,
460		,
461	$CH_2CH_2CH_2C(O)N(CH_2Ph)_2$	,

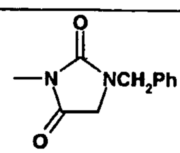
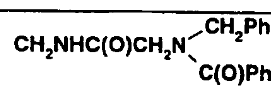
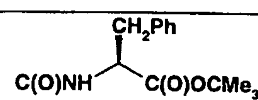
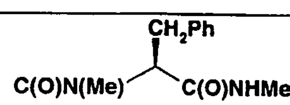
462		, or
463	$CH_2CH_2C(O)N(CH_2Ph)_2$	.

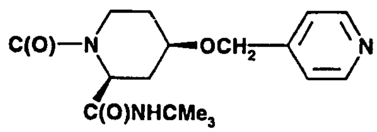
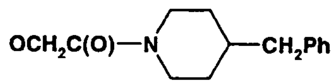
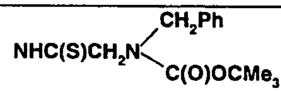
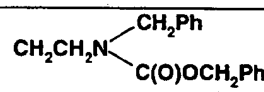
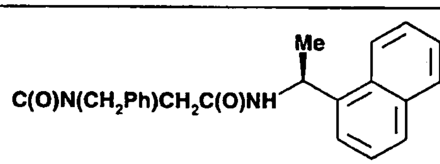
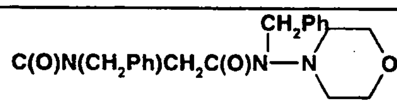
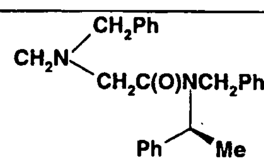
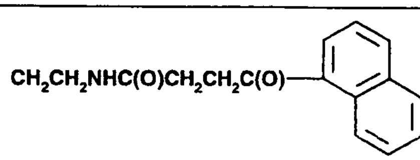
19. A compound according to claim 18 selected from the group consisting of entry numbers 407, 412, 413, 427 and 438.

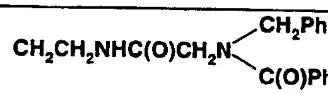
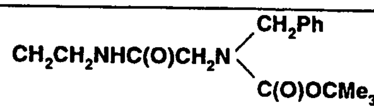
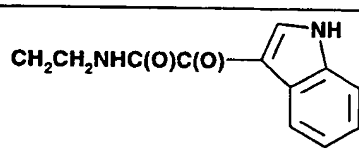
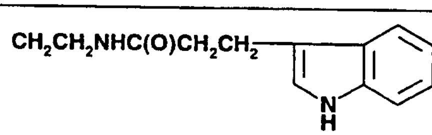
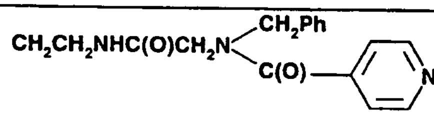
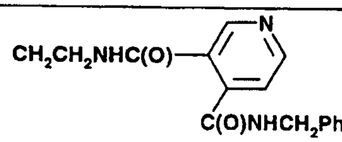
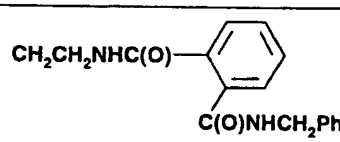
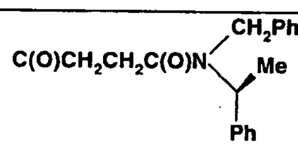
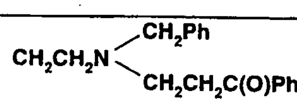
20. A compound according to claim 1, subsection (iii), having the structure

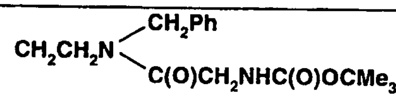
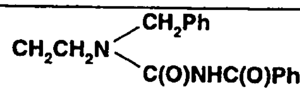
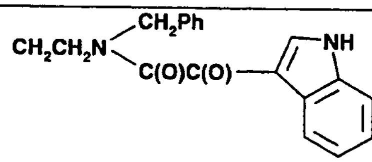
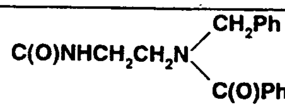
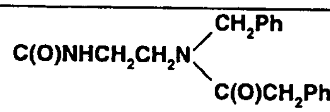
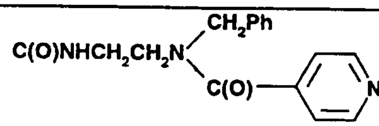
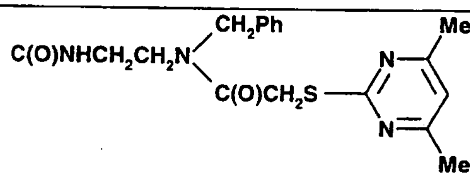
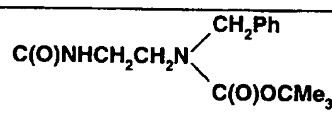
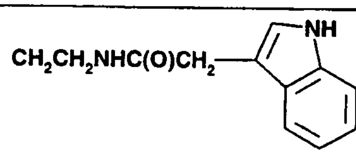
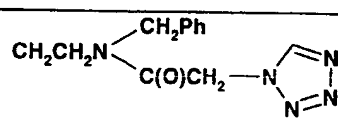


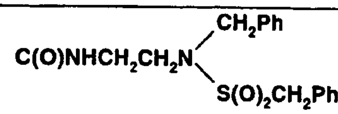
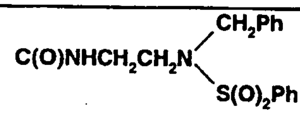
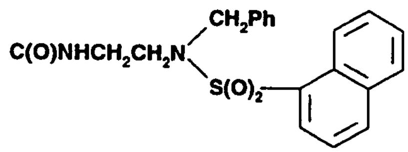
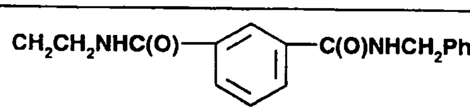
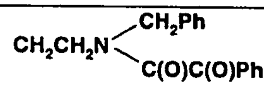
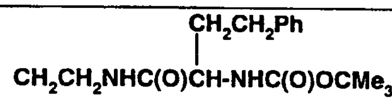
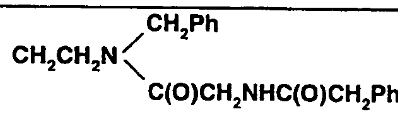
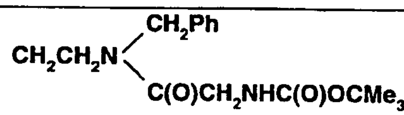
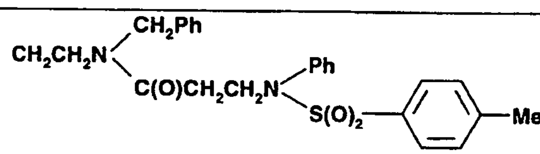
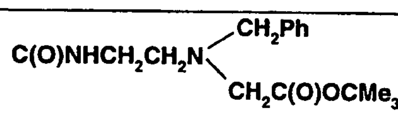
wherein Z is designated as follows:

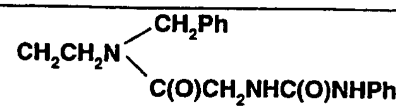
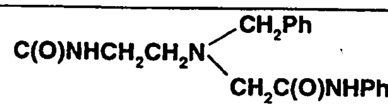
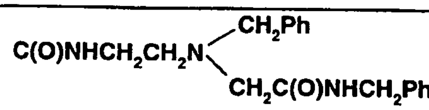
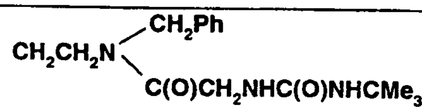
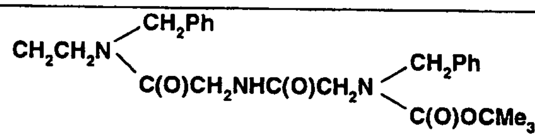
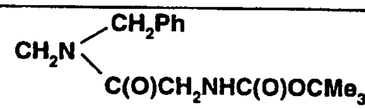
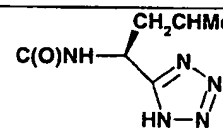
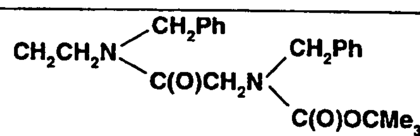
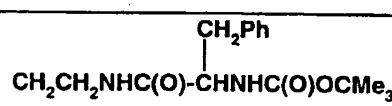
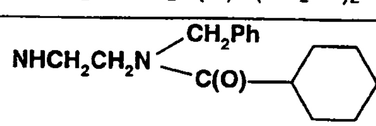
Table 5 Entry No.	Z	
501	$NHCH_2C(O)N(Me)CH_2Ph$	,
502	$NHCH_2C(O)NHCH_2Ph$	,
503		,
504		,
505		,
506		,

507		,
508		,
509	$OCH_2C(O)N(Me)CMe_3$	,
510	$OCH_2C(S)NHCH_2Ph$	,
511		,
512		,
513	$NHC(S)NHCH_2Ph$	,
514		,
515		,
516	C(O)OMe	,
517	$CH_2CH_2NH\text{-}S(O)_2\text{-}CH_2Ph$	,
518		,
519	$CH_2CH_2NHC(O)CH_2CH_2C(O)Ph$	,
520		,

521		,
522		,
523		,
524		,
525	$CH_2CH_2N(CH_2Ph)C(O)CH_2Ph$	,
526	$CH_2CH_2N(CH_2Ph)S(O)_2CH_2Ph$	,
527		,
528		,
529	$CH_2CH_2NHC(O)CH_2CH_2C(O)NHCH_2Ph$	,
530		,
531		,
532		,

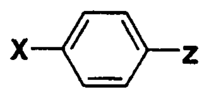
533		,
534		,
535	$CH_2CH_2NHC(O)CH_2NHC(O)OCMe_3$	,
536		,
537		,
538		,
539		,
540		,
541		,
542		,
543		,

544		,
545		,
546		,
547		,
548		,
549	$CH_2CH_2NHCH_2C(O)N(CH_2Ph)_2$	,
550		,
551		,
552		,
553		,
554		,

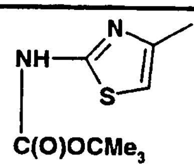
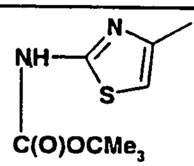
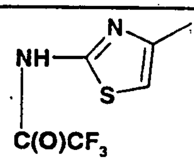
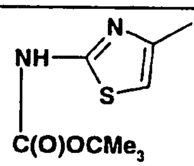
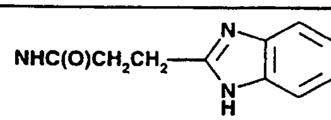
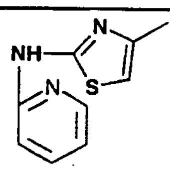
555		,
556		,
557		,
558		,
559		,
560		,
561		,
562		,
563		,
564	$CH_2NHCH_2C(O)N(CH_2Ph)_2$	, or
565		.

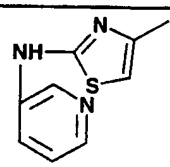
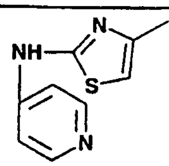
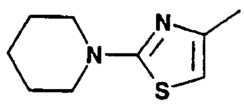
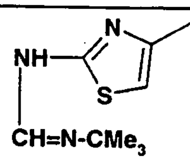
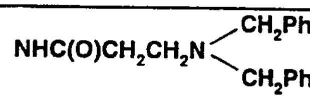
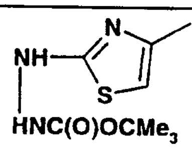
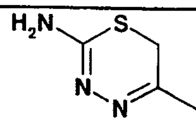
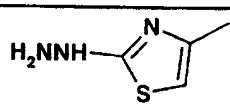
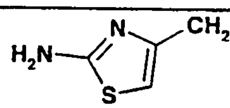
21. A compound according to claim 20 selected from the group consisting of entry numbers 511 and 536.

22. A compound according to claim 1, subsection (iv), having the structure

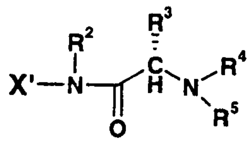


wherein X and Z are designated as follows:

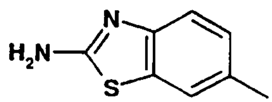
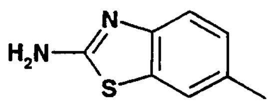
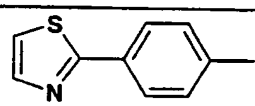
Table 6 Entry No.	X	Z	
603		NHC(O)NH-CHPr$_2$	,
604		NHC(S)NBu$_2$	,
605		NHC(O)NBu$_2$	,
606			,
607		NHC(O)NBu$_2$	,

608		NHC(O)NBu₂	,
609		NHC(O)NBu₂	,
610		NHC(O)NBu₂	,
611			,
612		NHC(O)NBu₂	,
613		NHC(O)NBu₂	,
614		NHC(O)NBu₂	, or
615		$NHC(O)CH_2CH_2N(CH_2Ph)_2$	.

23. A compound according to claim 1, subsection (v), having the structure

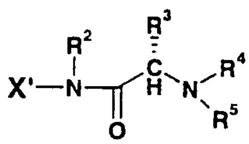


wherein R^2 is H, R^3, R^4 and R^5 and X' are designated as follows:

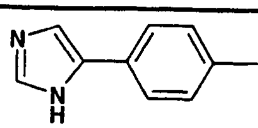
Table 7 Entry No.	X'	R^3	R^4	R^5
701		H	CH_2Ph	$C(O)OCMe_3$
703		CH_2Ph	H	$C(O)OCMe_3$
704		CH_2Ph	H	$C(O)OCMe_3$

, , or .

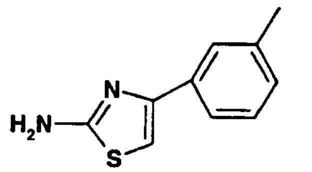
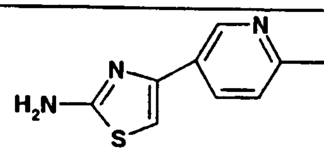
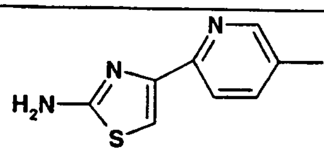
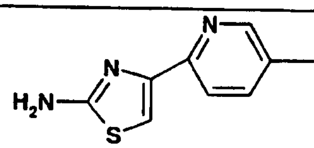
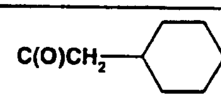
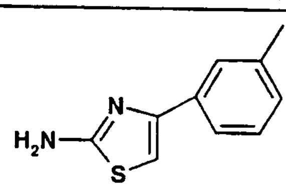
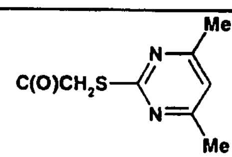
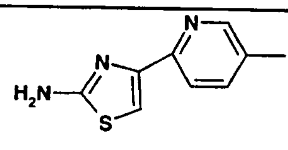
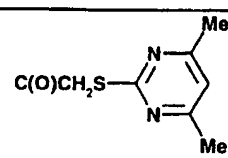
24. A compound according to claim 1, subsection (i), having the structure



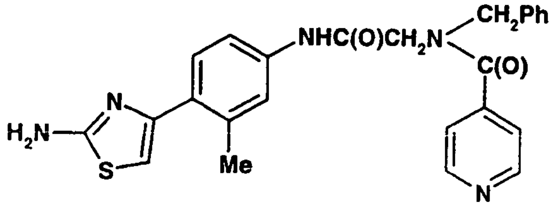
wherein R^2 is H, R^3, R^4 and R^5 and X' are designated as follows:

Table 7 Entry No.	X'	R^3	R^4	R^5
702		CH_2 Ph	H	$C(O)OCMe_3$

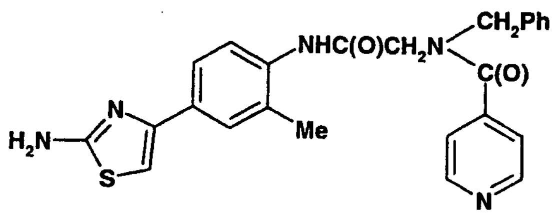
,

705		H	H	CH_2Ph	,
706		H	CH_2Ph	$C(O)OCMe_3$	,
707		H	CH_2Ph	$C(O)OCMe_3$	,
708		H	CH_2Ph		,
709		H	CH_2Ph		, or
710		H	CH_2Ph		.

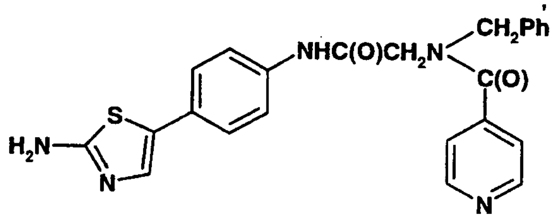
25. A compound according to claim 1, subsection (i), having the formula



,



, or



26. A method for treating herpes infection in a mammal comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically acceptable carrier and a compound according to claim 1.

27. A pharmaceutical composition comprising the compound according to claim 1 and pharmaceutically acceptable carrier.

28. The pharmaceutical composition according to claim 27, wherein the composition is suitable for oral administration.

29. The pharmaceutical composition according to claim 27, wherein the composition is suitable for topical administration.

30. A method for treating herpes infection in a mammal comprising the step of administering to a mammal in need of such treatment a therapeutically effective amount of the pharmaceutical composition according to claim 28.

31. A method for treating herpes infection in a mammal comprising the step of administering to a mammal in need of such treatment a

therapeutically effective amount of pharmaceutical composition according to claim 29.

INTERNATIONAL SEARCH REPORT

Inte :onal Application No
PCT/CA 99/01066

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/40 C07D417/12 C07D263/48 C07C275/24 A61K31/426
A61K31/427 A61K31/421 C07D233/61 C07D285/16 C07D417/04
C07C311/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 24343 A (BOEHRINGER INGELHEIM CA LTD ;BOEHRINGER INGELHEIM PHARMA (US)) 10 July 1997 (1997-07-10) cited in the application claims	1-31
X	F.C. SPECTOR ET AL: "Inhibition of Herpes Simplex virus replication by a 2-amino thiazole via interactions with the helicase component of the UL5-UL8-UL52-COMPLEX" JOURNAL OF VIROLOGY., vol. 72, no. 9, September 1998 (1998-09), pages 6979-6987, XP002128325 THE AMERICAN SOCIETY FOR MICROBIOLOGY., US ISSN: 0022-538X cited in the application the whole document	1-31

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 January 2000	11/02/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/01066

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 045 081 A (CIBA GEIGY AG) 3 February 1982 (1982-02-03) claims ---	1-31
A	FR 2 754 258 A (SANOFI SA) 10 April 1998 (1998-04-10) claims ---	1-31
P,X	WO 99 42455 A (TULARIK INC) 26 August 1999 (1999-08-26) claims -----	1-31

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 99/01066

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 30-31
are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 99/01066

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